ARCHIVES OF PATHOLOGY

Volume 33
1942

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

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VOLUME 33 JANUARY 1942 NUMBER 1

EXPERIMENTAL STUDIES IN CARDIOVASCULAR PATHOLOGY

IV. METHYL CELLULOSE ATHEROMATOSIS AND THESAUROSIS

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In previous studies it was shown that the repeated and prolonged parenteral introduction of highly excessive amounts of a chemically relatively inert macromolecular substance, polyvinyl alcohol, into rats, rabbits and dogs leads in these species to the development of a polyvinyl alcohol thesaurosis and widespread polyvinyl alcohol atheromatosis (Hueper [1]; Hueper, Landsberg and Eskridge [2]). The morphologic changes observed markedly resemble the organic lesions found in man in disturbances of the lipoid metabolism and particularly in cholesterol atheromatosis. In the present report the toxicopathologic investigations on megalomolecular compounds are extended to a study of the hematologic and organic effects produced by the intravenous injection of another highly polymerized carbohydrate, methyl cellulose. A solution of this substance is an osmotically active colloidal agent suitable for the treatment of experimental shock as a substitute for plasma (Hueper, Martin and Thompson [3]).

EXPERIMENTAL PROCEDURE

Methyl cellulose is the methyl ether of cellulose and consists of polymerized dextrose molecules. It is one of the more recently developed dispersing, thickening, emulsifying, sizing and coating agents extensively used in the cosmetic and pharmaceutic industries as a substitute for mucilages and employed in numerous additional roles in many other manufactures (grease-proof coating of paper, adhe-

From the Warner Institute for Therapeutic Research.

1. Hueper, W. C.: Arch. Path. **28**:510, 1939; **31**:11, 1941; The Etiology and the Causative Mechanism of Arteriosclerosis and Atheromatosis, Medicine, to be published.

2. Hueper, W. C.; Landsberg, J. W., and Eskridge, L. C.: J. Pharmacol. & Exper. Therap. **70**:201, 1940.

3. Hueper, W. C.; Martin, G. J., and Thompson, M. R.: The Treatment of Shock by the Intravenous Administration of Nonhematogenous Macromolecular Substances, Am. J. Surg., to be published.

sive, soaps, paints, pastes and textiles). It is a white fibrous fluffy material which when dissolved in water gives a water-clear colorless viscous colloidal solution having a neutral reaction. The degree of viscosity of a methyl cellulose solution depends not only on the concentration but also on the degree of polymerization of the particular type of methyl cellulose used. Methyl cellulose solution (methocel, Dow Chemical Company) is offered in seven different grades of viscosity, ranging from 15 to 4,000 centipoises for a 2 per cent solution. Aqueous solutions of methyl cellulose gel when heated above 40 C. and at higher temperatures and moderately high concentrations give milky white coagulums. This reaction, however, is reversible on cooling and can be prevented by the addition of soluble salts of iodides and thiocyanates, agents which, incidentally, also hinder the precipitation and deposition of lipids and thereby the formation of atheromas in rabbits subjected to an excessive ingestion of cholesterol. Methyl cellulose is, moreover, coagulated from its aqueous solutions by highly concentrated solutions of various salts. The methyl cellulose used in these experiments is of a highly viscous variety (400 centipoises) and is precipitated completely by the addition of ammonium sulfate in amounts which produce the same effect on the euglobulins of the blood plasma. Concentrated inorganic and organic acids display a similar action on solutions of methyl cellulose. These are miscible with moderate amounts of propylene glycol and ethyl alcohol, while methyl alcohol and glycerol cause the appearance of slight opalescence and the formation of a soft gelatinous mass. The molecular weight of methyl cellulose varies with the degree of polymerization and for the medium viscous variety is approximately 50,000 when calculated according to the Staudinger formula on the relationship between the viscosity of long-chained polymerized compounds and their molecular weight. A solution of methyl cellulose mixed with a solution of gelatin or with blood plasma forms an emulsion (Heller[4]) which can be broken by high speed centrifugation.

For the purpose of the experiment methyl cellulose in concentrations of 2 and 5 per cent in physiologic solution of sodium chloride was injected intravenously into rabbits and dogs. A 0.25 per cent solution of this particular type of methyl cellulose has a viscosity of 2, which is equal to the average viscosity of normal human or canine plasma. The following hematologic observations were made in the acute as well as in the chronic experiments: hemoglobin content, number of erythrocytes, polychromasia, irregularity in erythrocytic cell size, percentage of reticulocytes, number of nucleated red cells, absolute erythrocytic cell size, erythrocytic fragility, volume of packed red blood cells, sedimentation rate, coagulation time, prothrombin time, viscosity of the whole blood and of the plasma, number of platelets, number of leukocytes, differential count and occasionally blood pressure. The weight was determined at weekly intervals.

ACUTE EXPERIMENTS

Three dogs were used for determining the acute effects which the intravenous injection of graduated doses (10 cc., 20 cc. and 30 cc.) of a 5 per cent methyl cellulose solution exerts on the blood. The 5 per cent solution was so highly viscous that it could be injected from a syringe through a 15 gage needle only by exerting considerable pressure. Blood was withdrawn for examination at intervals of five, fifteen and thirty minutes, two, five and twenty-four hours, and four, six,

4. Heller, W.: Compt. rend. Soc. de biol. **207**:1046, 1938.

TABLE 1.—*Acute Hematologic Effects of Methyl Cellulose in Dog 426*

Time	Erythrocytes, Millions	Nucleated Erythrocytes, per Cent	Reticulocytes, per Cent	Volume of Packed Erythrocytes, Mm.	Sedimentation Rate, Mm.	Hemoglobin, Gm.	Coagulation Time	Prothrombin Time	Viscosity		Platelets	Leukocytes, Thousands	Polymorphonuclears		Eosinophils, per Cent	Lymphoid Cells, per Cent
									Whole Blood	Plasma			Mature, per Cent	Immature, per Cent		
Before.....	7.28	..	6.1	54.0	1.5	14.8	8.25 sec.	10 sec.	6.16	2.03	80.0	7.20	62	25	3	10
5 min.....	6.75	..	6.3	52.0	20.0	14.0	70 min.	5 sec.	14.16	5.34	280.0	3.00	38	16	4	43
10 min.....	6.43	2	6.8	49.5	28.0	14.2	60 min.	3 sec.	10.04	4.77	140.0	2.40	28	41	2	29
30 min.....	6.60	3	6.7	51.0	17.0	16.4	60 min.	2 sec.	9.04	4.25	105.0	3.20	32	30	4	34
2 hr.....	6.91	1	6.7	52.5	22.0	14.8	.....	.....	....	....	.....	9.30	50	36	1	13
5 hr.....	6.74	2	7.0	49.5	32.0	14.0	36 min.	3 sec.	6.50	3.50	310.0	14.10	49	47	1	3
24 hr.....	7.10	1	7.1	48.0	25.0	14.2	11 min.	7 sec.	8.12	3.58	220.0	19.40	81	16	2	1
4 days.....	8.10	..	7.2	57.0	1.5	16.4	17 min.	8 sec.	8.60	2.78	84.0	14.80	59	36	2	3
6 days.....	7.13	..	7.3	47.0	25.0	14.2	44 min.	20 sec.	5.80	2.48	270.0	10.90	59	23	5	13
11 days.....	6.85	..	7.1	47.0	31.0	13.9	29 min.	22 sec.	5.66	2.28	340.0	8.80	43	39	6	12

eleven and eighteen days. The effects obtained in many respects followed in degree the dose administered. Table 1 shows the data recorded for the dog given the largest amount (30 cc.).

The data presented in table 1 show that the drop in the number of erythrocytes, in the volume of packed red blood cells and in the amount of hemoglobin following the injection of the methyl cellulose solution used is representative of the mild hemodilution caused by the osmotic activity of the macromolecular matter introduced into the blood. This reaction lasts approximately twenty-four hours. The recovery of the hemoglobin, however, occurs at a somewhat slower rate. During the period of recovery, nucleated erythrocytes appear in the blood. This stage is followed on the fourth day by a brief transitory increase in the number of erythrocytes above the original level. By the sixth day normal erythrocytic values have been reached again. The hemoglobin value as well as the volume of the packed red cells, on the other hand, continue to remain lower than originally. The sedimentation of the erythrocytes is markedly accelerated immediately after the injection of the methyl cellulose solution and does not change appreciably thereafter within the following eighteen days, showing a normal level only during a brief transitory episode of hemoconcentration on the fourth day. A similar course is taken by the coagulation time, which is markedly lengthened. The prothrombin time, on the other hand, is considerably shortened and shifts back to approximately normal values only after a twenty-four hour period. There is then an appreciable lengthening of the prothrombin time for the remainder of the observation period. The viscosity of the blood is more than doubled immediately after the injection of the methyl cellulose solution and then drops rapidly within five hours to almost normal values. It rises again, however, to increased values and returns to the normal range only after six days. The viscosity of the plasma shows a similar marked initial increase but drops gradually without undergoing any fluctuations, such as those observed with the whole blood, reaching at the end of the observation period still slightly elevated values. The platelets are increased in number after the injection of the methyl cellulose solution and remain at such levels with the exception of an erythrocytotic episode, when their number is normal. The leukocytes exhibit a marked leukopenic reaction directly after the introduction of methyl cellulose. This response lasts for less than two hours and is followed by leukocytosis, which persist, for about four days. The leukocytes return to normal limits thereafter. The lymphocytes are relatively increased in number during the leukopenic phase and are decreased in number during the leukocytotic stage. There is an apparent transitory increase in the number of immature myeloid leukocytes during the leukopenic episode.

CHRONIC EXPERIMENTS

Chronic experiments consisting of the repeated and prolonged intravenous injection of a 2 per cent methyl cellulose solution into 3 rabbits and 7 dogs furnished the material for additional hematologic studies as well as for subsequent morphologic investigations on animals which either died from the results of the treatment received or were killed for the purpose of these examinations.

The 3 rabbits were given 25 cc. of the methyl cellulose solution twice weekly. Two of them died early in the experiment (sixth day and ninth day) from infectious colitis, while the third rabbit survived for ninety days. The 2 rabbits which died first showed at autopsy evidence of colitis and congestion of the lungs. Their spleens, livers and kidneys were of normal size and appearance. However, the kidneys of the rabbit which died after nine days each exhibited a grayish green cortex. The rabbit which died ninety days after the start of the experiment had a dark red, enlarged liver showing a distinct white-yellow network. The spleen was dark red, firm and three times the normal size.

Three of the dogs, which weighed at the start of the experiment from 9.1 to 12.8 Kg., were given 25 cc. of a 2 per cent methyl cellulose solution twice during the first week, 60 cc. twice weekly during the following three weeks and 120 cc. three to five times weekly during the remainder of the experiment. One of these dogs died fifty-seven days after the start of the experiment, having received a total of 2,115 cc. of the methyl cellulose solution, or 42 Gm. of methyl cellulose. The second dog survived for sixty-six days and had received at the time of its death 2,930 cc. of methyl cellulose solution, equivalent to 60 Gm. of methyl cellulose. The third animal was killed on the eighty-third day of the experiment, after the administration of a total of 3,375 cc. of methyl cellulose solution, representing 67 Gm. of methyl cellulose. Two additional dogs died after twelve and thirteen days, respectively, during which time they had received a total of 1,040 cc. of methyl cellulose solution (21 Gm. of methyl cellulose) in individual doses of 130 cc. The sixth dog died on the sixth day, after the injection of a total of 260 cc. of methyl cellulose solution (5 Gm.). The seventh dog, which is still alive, was given in the beginning daily five times a week 65 cc. of a 2 per cent methyl cellulose solution. After four injections the treatment was discontinued for two weeks and was then resumed and has been carried on for a total of four months. The dog is apparently healthy, has a good appetite and has gained in weight. The weight curve of the other 6

dogs showed in the beginning of the experiment usually a moderate gain in weight and some time before death a progressive loss to the extent that 3 of the dogs died with an actual loss in weight. It was noticed that bleeding of the gums developed in several dogs during the course of treatment. There were no appreciable changes in blood pressure in several of the dogs examined during an advanced stage of the administration of methyl cellulose. The blood pressure in the femoral artery was determined repeatedly.

The postmortem examination of the 6 dogs showed that the spleens were always markedly enlarged; those of 4 dogs, which had received from 42 to 67 Gm. of methyl cellulose, ranged from 230 to 400 Gm. in weight. Some spleens were reddish with grayish granulations. Most of them were firm and friable. On the other hand, the spleen which weighed 400 Gm. was brownish yellow and had a very soft, almost liquid pulp. The livers were firm, moderately to markedly enlarged and weighed up to 760 Gm. Their color was reddish grayish brown, and their cut surfaces exhibited a grayish network. The kidneys were large, and each had a greenish brown cortex. The inguinal and retroperitoneal lymph nodes were moderately enlarged and of brown to greenish brown color. The lungs were congested. The hearts were contracted, and the brains were normal.

Table 2 presents the hematologic data obtained on a single dog, which may serve as representative of the entire series.

The blood counts were made before the injections of the methyl cellulose so that at least twenty-four hours had elapsed between the last injection of solution and the withdrawal of blood for hematologic study. Analysis of the data presented in table 2 shows that there occurred with the progress of the intravenous administration of the methyl cellulose solution a decrease in the amount of hemoglobin, in the number of erythrocytes and in the volume of packed red blood cells. At the same time the viscosity of the whole blood and, to an even greater degree, that of the plasma became markedly increased. These increases persisted for some time; a gradual decrease was observed when the treatment was temporarily discontinued. The short transitory drops in blood viscosity occurring while the treatment was going on were apparently results of episodes of marked osmotic hemodilution. The reticulocytes varied between 6.5 and 7.6 per cent. There were no appreciable fluctuations in the observed size of the eythrocytes. The sedimentation of the erythrocytes was considerably accelerated, whereas the coagulation time was in general more or less markedly lengthened. The prothrombin time exhibited also a tendency to be lengthened. The

TABLE 2.—*Chronic Hematologic Effects of Methyl Cellulose in Dog 427*

Day of Experiment	Total Dose of Methyl Cellulose, Cc. of 2% Solution	Erythrocytes, Millions	Hemoglobin, Gm.	Volume of Packed Erythrocytes, Mm.	Leukocytes, Thousands	Platelets	Coagulation Time, Min.	Sedimentation Rate, Mm.	Prothrombin Time, Sec.	Viscosity at 20 C.	
										Whole Blood	Plasma
1	0	6.03	13.0	47.0	15.8	30,000	18.5	29	10	5.26	2.13
2	50	6.08	12.7	43.0	17.6	306,000	18.0	43	14	5.70	2.50
13	..	6.10	12.7	45.5	8.3	250,000	14.5	32	21	5.46	2.23
14	75	5.70	12.7	43.0	12.0	288,000	32.25	30	20	5.24	2.18
15	135	5.64	12.3	42.0	8.4	140,000	5.2	44	20	4.92	2.34
16	195	5.71	12.7	43.0	10.7	135,000	7.0	43	20	7.00	2.74
19	220	6.15	13.2	47.0	14.7	140,000	36.0	35.2	22	6.52	2.74
21	340	6.31	12.8	44.5	10.8	220,000	30.0	33.0	11	7.54	3.76
23	460	5.94	12.8	44.5	12.6	210,000	74.0	30.0	16	9.54	5.00
26	520	5.74	11.8	41.0	10.3	270,000	44.0	48.5	19	6.48	3.43
28	640	5.37	11.2	41.5	8.7	130,000	12.0	30.5	20	7.00	4.43
30	700	4.83	10.9	38.5	10.2	330,000	66.0	52.0	19	7.28	4.07
33	760	5.25	11.5	39.0	9.7	260,000	62.0	48.5	21	6.50	3.58
36	1,000	4.67	10.8	38.5	9.6	310,000	49.0	36.5	34	7.34	4.34
38	1,240	4.74	10.5	38.5	8.8	180,000	50.0	22.0	18	9.00	5.63
40	1,360	5.25	11.7	37.0	5.95	140,000	26.0	54.0	17	5.60	2.87
44	1,500	4.71	8.7	31.0	15.6	250,000	39.0	34.0	17	8.98	7.74
51	1,980	4.39	8.4	28.5	16.4	340,000	31.0	63.0	23	9.00	8.60
58	.....	4.71	9.4	32.5	14.8	170,000	76.0	59.0	19	5.74	3.08
64	.....	5.39	10.6	38.5	12.8	208,000	47.0	25.5	..	5.08	2.66
71	.....	5.70	12.3	42.0	14.7	290,000	4.0	2.0	..	5.96	2.54
78	2,630	4.21	8.8	30.0	10.7	120,000	6.0	31.0	..	7.74	4.20

platelets remained within normal limits. While the leukocyte counts fluctuated within normal limits, there developed eosinophilia ranging from 3 to 10 cells. There was, moreover, a moderate increase in the number of immature neutrophilic leukocytes during the more advanced part of the experimental period.

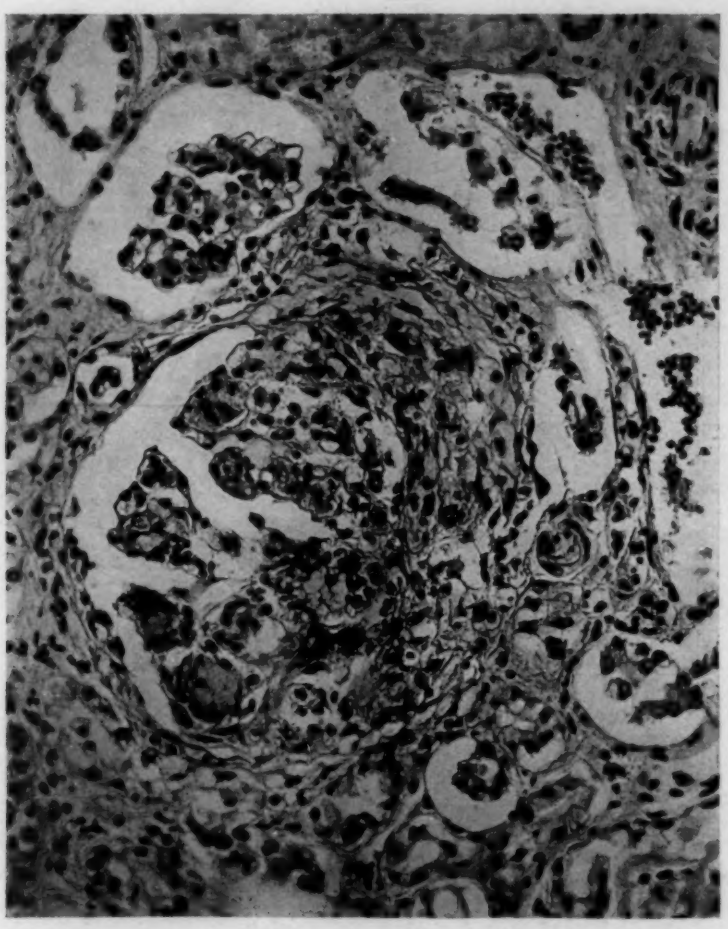

Fig. 1.—Kidney of a rabbit showing foam cell swelling of the endothelium of the glomerular capillaries, which form club-shaped loops and which are in places adherent to Bowman's capsule; × 300.

The histologic examination of the organs of the rabbits and of the dogs gave the following results: In animals given relatively small amounts of methyl cellulose, i. e., the rabbits which died within the first

week of the experiment from an incidental infection, there were either no organic changes present or only minor ones affecting mainly the renal glomeruli. These showed in some instances a few small granulomatous formations with giant cells or a cystic distention of the glomerular capillaries, and such capillaries had partly hyalinized and

Fig. 2.—Aorta of a dog showing a thick cushion-like proliferation of foam cells containing apparently methyl cellulose; × 120.

thickened walls (fig. 1). The tubular lumens of the dogs which died during an early stage of the administration of methyl cellulose contained scanty precipitations of a greenish blue matter, while the glomeruli were essentially normal. The spleens of these animals were converted into accumulations of multinucleated giant cells embedded into a necrotic matrix.

The organs of the 4 dogs and of the 1 rabbit which received methyl cellulose over a prolonged period displayed, on the other hand, a great variety of lesions. While all the brains showed a normal brain substance, the choroid plexus and the pituitary of 1 animal contained small foci of foam cells. The lungs showed interstitial cells exhibiting a peculiar

Fig. 3.—Aorta of a dog covered by a thick foam cell intimal coating and containing a large calcified necrotic focus in the media; × 150.

empty cytoplasm. A small foam cell cushion was present in the epicardial coronary artery of 1 dog, whereas all the dogs had normal myocardiums. The aortas invariably exhibited, especially in the supravalvular portion, either a diffuse and relatively thick intimal coating of foam cells or several large foam cell nodules. The media underneath these lesions often contained large focal hyaline necroses and calcifications (figs. 2 and 3). Similar intimal changes were found to a lesser degree

in the pulmonary artery and in several other large arteries of the elastic type. The aortas of the rabbits exhibited more chronic atheromatous lesions, as the foam cell cushions contained appreciable numbers of fibroblasts (fig. 4). The livers of the rabbits showed the parenchyma converted into a structure composed entirely of large, swollen, light-

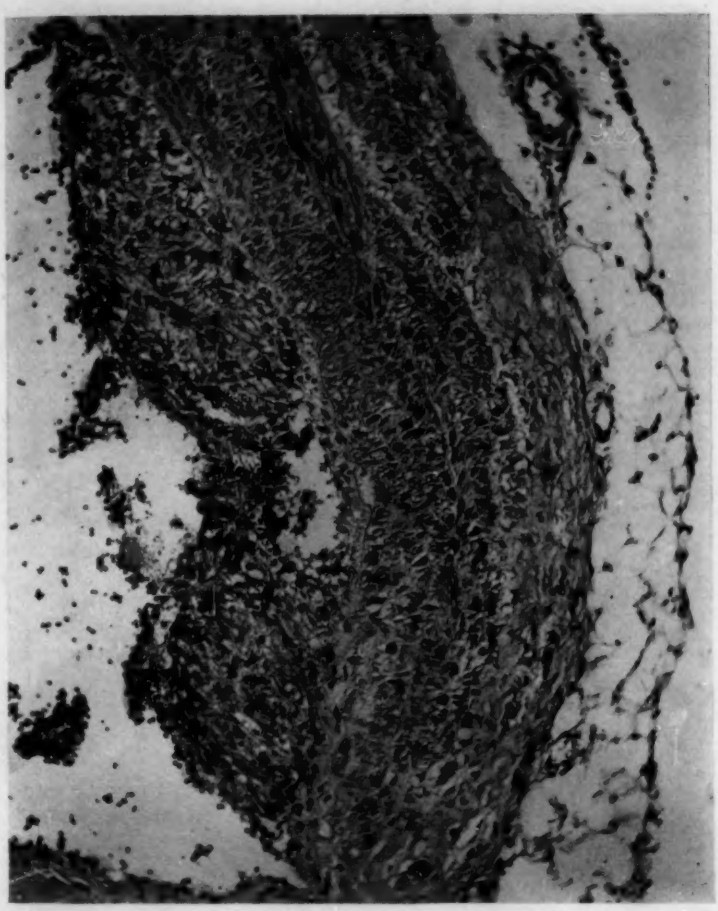

Fig. 4.—Aorta of a rabbit displaying two nodular foam cell intimal proliferations containing a moderate number of fibroblasts; × 120.

colored cells having a granular cytoplasm. The livers of the dogs showed large, ill defined areas of similar liver cells interspersed with strands and groups of apparently well preserved liver cells (fig. 5). The capillary endothelium of the livers appeared to be intact. In some areas, however, there was some indication that Kupffer cells had under-

gone foam cell changes. The pulp of the spleens was transformed into a foam cell structure containing numerous small foci of multinucleated, indistinctly outlined giant cells (fig. 6). The splenic follicles were small, and the walls of the splenic arteries were markedly vacuolated. Some of the retroperitoneal lymph nodes were normal, while others

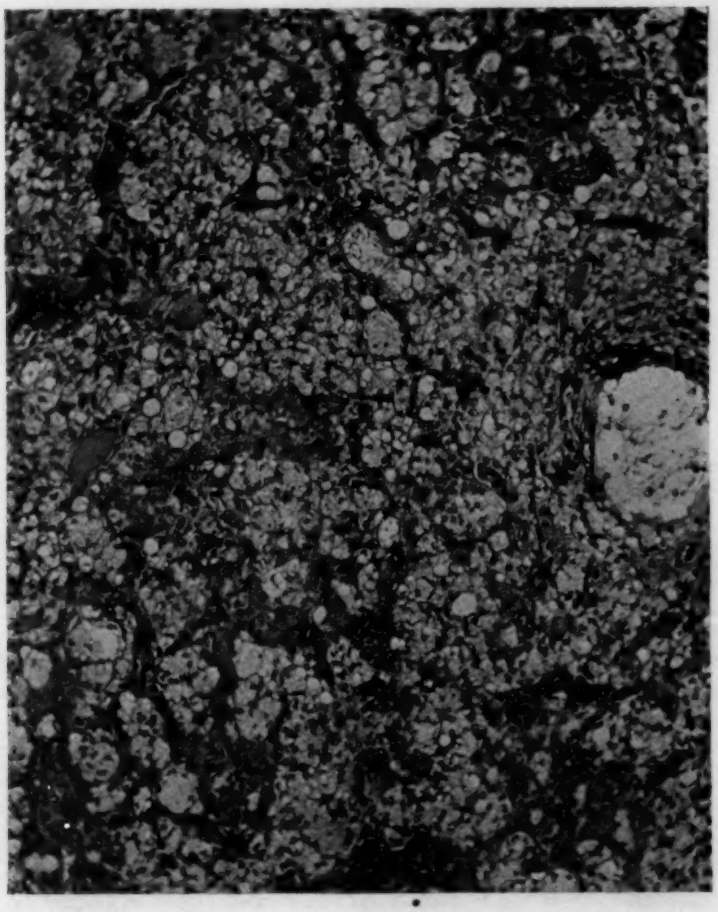

Fig. 5.—Liver of a dog showing a diffuse foam cell transformation of the hepatic parenchyma, which is permeated by isolated strands and groups of dark-stained intact liver cells; × 130.

contained masses of foam-cellular histiocytic cells. The kidneys were altered as follows: The medial coats of the main renal artery and its intrarenal branches often showed marked vacuolation. The glomerular capillaries contained a few to many foam-cellular endothelial cells, which

sometimes obliterated the capillary lumens. There were scattered small interstitial foci foam cells present in the renal parenchyma. The tubules exhibited atrophic and degenerative changes, especially where these structures were embedded in a myxomatoid interstitial tissue. The adrenals were in general normal. The testes of several animals exhibited

Fig. 6.—Diffuse foam cell transformation of the splenic pulp of a dog with an isolated large foam-cellular multinucleated giant cell; × 280.

marked degenerative changes of the spermatogenic epithelium, characterized by the appearance of spermatid giant cells and a partial collapse of the tubules. In the venous plexus of the spermatic cord of 1 dog there were granulomas of multinucleated giant cells and foam cells

filling a part of the vascular lumens (fig. 7). The wall of the small intestine of 1 dog displayed an accumulation of foam cells in the submucosa and mucosa. No morphologic abnormalities were seen in the thyroids, parathyroids, stomachs, pancreases, ovaries, uteri, bladders and prostates.

Fig. 7.—Testis of a dog displaying moderate degeneration of the spermatogenic epithelium and collapse of some of the spermatogenic tubules in addition to a foam-cellular and giant-cellular granulomatous proliferation within the lumen of a peritesticular vein; × 110.

Sections of the atheromatous aortas which were stained with sudan III showed that the foam cell lesions were free from fatty substances.

COMMENT

The hematologic and anatomic reactions following the acute, as well as the prolonged and excessive, intravenous injection of solutions of methyl cellulose resemble in many respects those described in connection with the clinical and experimental use of solutions of acacia and with the experimental parenteral introduction of polyvinyl alcohol or other macromolecular substances, such as pectin, glycogen and starch. The responses elicited in the blood by methyl cellulose and the other macromolecular substances mentioned are apparently due in part to a physicochemical disturbance produced in the equilibrium of the colloidal macromolecular substances in the plasma and in part to the interference with the vital activities of various organs in which the methyl cellulose is retained and which normally supply cellular elements as well as chemical constituents such as, especially, plasma proteins to the blood.

The reduction in the number of erythrocytes is thus in part an apparent decrease, the result of osmotic hemodilution, and in part an actual decrease, due to the pathologic changes produced in the liver and the spleen. The leukopenic episodes, as well as the acceleration of the erythrocytic conglomeration and sedimentation and the delay of blood coagulation, are evidently manifestations of the abnormal colloidal status of the blood, which finds an additional and striking expression in the increased viscosity of the whole blood and particularly of the plasma.

The anatomic lesions observed are of two types: (1) storage of methyl cellulose in various organs with reactive cellular changes and (2) atheroma formation in the arterial vessels. The retention of methyl cellulose in the spleen, liver, lymph nodes and kidneys gives rise to tissue changes which are characteristic of a thesaurosis. The apparent inability of the organisms to degrade metabolically the large molecules of methyl cellulose so that they can pass readily through the capillary filtration membranes and thus be eliminated from the body in large amounts and in rapid fashion is responsible for this phenomenon. The organic reactions elicited by the retained material resemble in many respects those produced by the storage of acacia and of glycogen. It is noteworthy in this connection that the various chemically different macromolecular substances giving rise to storage phenomena display a certain affinity to different organs and cellular components of organs. While polyvinyl alcohol is never stored in the liver cells but may be retained in the ganglion and glia cells of the brain, methyl cellulose, which does not seem to enter the nerve cells, is stored readily, like acacia, in the liver cells. The reactive vascular manifestations elicited by methyl cellulose consist in part of endothelial proliferations with giant cell formation, representing a foreign body type of reaction. Such changes occur in the

glomerular capillaries and occasionally in the peritesticular venous plexus. They are caused apparently by the presence of large accumulations of methyl cellulose within the vascular lumens. The more frequent and generally more important vascular lesions produced by methyl cellulose are represented by endothelial proliferations of foam cell character and atheromatous type. Inasmuch as these lesions are free from fatty substances, it seems to be reasonable to conclude that they contain methyl cellulose and that thus the methyl cellulose atheroma is the morphologic equivalent of the normal or experimental cholesterol atheroma and of the experimental polyvinyl alcohol atheroma. The frequent concurrence of medial hyalinization and calcification beneath such intimal lesions indicates that these changes seem to interfere with the proper nutrition of the medial portion of the arterial wall. Such an action mechanism of methyl cellulose accumulations appears to be probable because of the resistance which films of this substance offer to the penetration of fatty substances. Measurements of the oxygenation speed of the blood of dogs subjected to prolonged intravenous treatment with methyl cellulose brought out the fact that there exists an appreciable interference with the speed but not with the amount of uptake of oxygen by erythrocytes in these animals, a condition similar to that existing in cholesterolized rabbits and polyvinylized dogs, which exhibit similar arterial changes (Hueper [3]; Martin and Hueper [5]). These observations suggest that substances circulating in the blood and similar in certain physicochemical qualities (chemical inertness, film formation, colloidal dispersion in the plasma, nonpenetrability to nutritive and metabolic elements) are capable of producing atheromatous arterial lesions by impairing the oxygenation and nutrition of the vascular wall. It must be emphasized that the various organic lesions mentioned are produced only when highly excessive amounts of methyl cellulose are introduced into the animal organism.

SUMMARY

The intravenous injection of a solution of methyl cellulose into dogs causes hematologic reactions which may be designated as the hematologic macromolecular syndrome (reduction in number of erythrocytes, in amount of hemoglobin, in volume of packed erythrocytes; acceleration of conglutination and sedimentation of erythrocytes; lengthened coagulation time; acute transitory leukopenia; persistent myeloid leukocytosis; increased viscosity of plasma).

The chemical inertness of the injected substance and the inability of the body to degrade the macromolecular compound and thereby to

5. Martin, G. J., and Hueper, W. C.: Biochemical Aspects of the Parenteral Administration of Macromolecular Substances: I. Polyvinyl Alcohol, to be published.

facilitate the elimination of the substance lead to retention and accumulation of methyl cellulose in the liver, spleen, lymph nodes, kidney and vascular walls (thesaurosis).

The arteries of rabbits and dogs given injections of a solution of methyl cellulose over long periods show extensive atheromatous changes of an apparently methyl cellulose nature. Medial degeneration and calcification appear underneath these intimal lesions.

Methyl cellulose atheromatosis is the result of an impairment of the oxygenation and nutrition of the vascular wall caused by the formation of methyl cellulose films on the surface of the intima and of the erythrocytes. This causative mechanism is common to the dynamics of atheromatosis in general.

MESONEPHROMA OF THE OVARY

FURTHER STUDIES

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During the last two decades there has been a great advance in the classification of ovarian tumors. This has largely been the result of increasing knowledge in endocrinology and mammalian embryology. In no branch of descriptive pathology has the study been more fruitful. One has but to read a textbook of thirty years ago to appreciate the many changes. For example, the classification "large round cell sarcoma" has now given way to "dysgerminoma," and many of the solid ovarian tumors in the miscellaneous groups can now be classified as granulosa cell tumor or as derivatives of that tumor, namely, thecoma and luteoma.

In spite of such advances, however, the present classification is unsatisfactory. Many tumors must still be grouped under the purely descriptive headings of solid adenocarcinoma, medullary carcinoma and the like. From this residue of ovarian tumors there is occasionally separated a group which can be described as an entity. Mesonephroma is the latest group to be so recognized. Whatever may be the ultimate fate of mesonephroma in the scheme of ovarian tumors, especially as regards its histogenesis, there can be little doubt that it is a pathologic unity.

In 1939 Schiller [1] described ten ovarian tumors which he classified separately and named mesonephroma. A year later we [2] described 6 similar tumors, and the present report deals with 9 additional ones. We shall mention briefly the 6 tumors previously reported in order to bring out certain features which further study of the tumors in this group has revealed (table).

DESCRIPTION

Grossly, the tumors classified as mesonephroma may be either semisolid or cystic. Schiller [1] pointed out that many of them were cystic, and that is certainly true. However, many more have solid areas, and

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From the Kelly Clinic and the Department of Gynecology of the Johns Hopkins Hospital and University.

Read before the Section on Pathology and Physiology at the Ninety-Second Annual Session of the American Medical Association, in Cleveland, June 5, 1941.

1. Schiller, W.: Am. J. Cancer **35**:1, 1939.
2. Jones, H. W., and Seegar, G. E.: Am. J. Obst. & Gynec. **39**:322, 1940.

some are practically all solid, except for areas which have become cystic apparently through necrosis and absorption of tissue. Mesonephroma presents the papillary tendency common to many ovarian tumors.

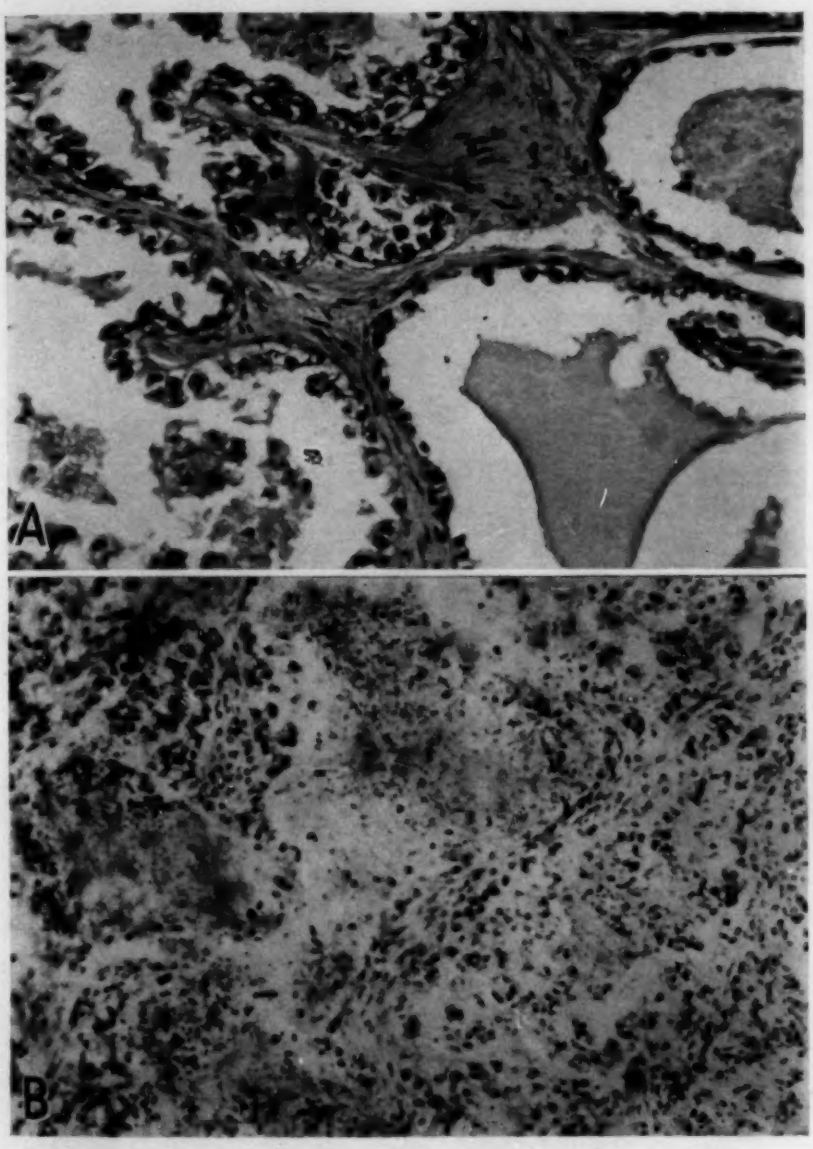

Fig. 1.—Low power photomicrographs. *A* shows the characteristic cystic spaces lined by a single layer of flattened endothelial-like cells with scanty cytoplasm and bulging nuclei (case 7). In the upper left hand space there is beginning proliferation which frequently causes an apparent resemblance to glomeruli. *B* shows the small cystic spaces filled by an overgrowth of cells (case 9).

Grossly, therefore, there are no features which distinguish it from other ovarian neoplasms. The diagnosis can be made only on the microscopic picture.

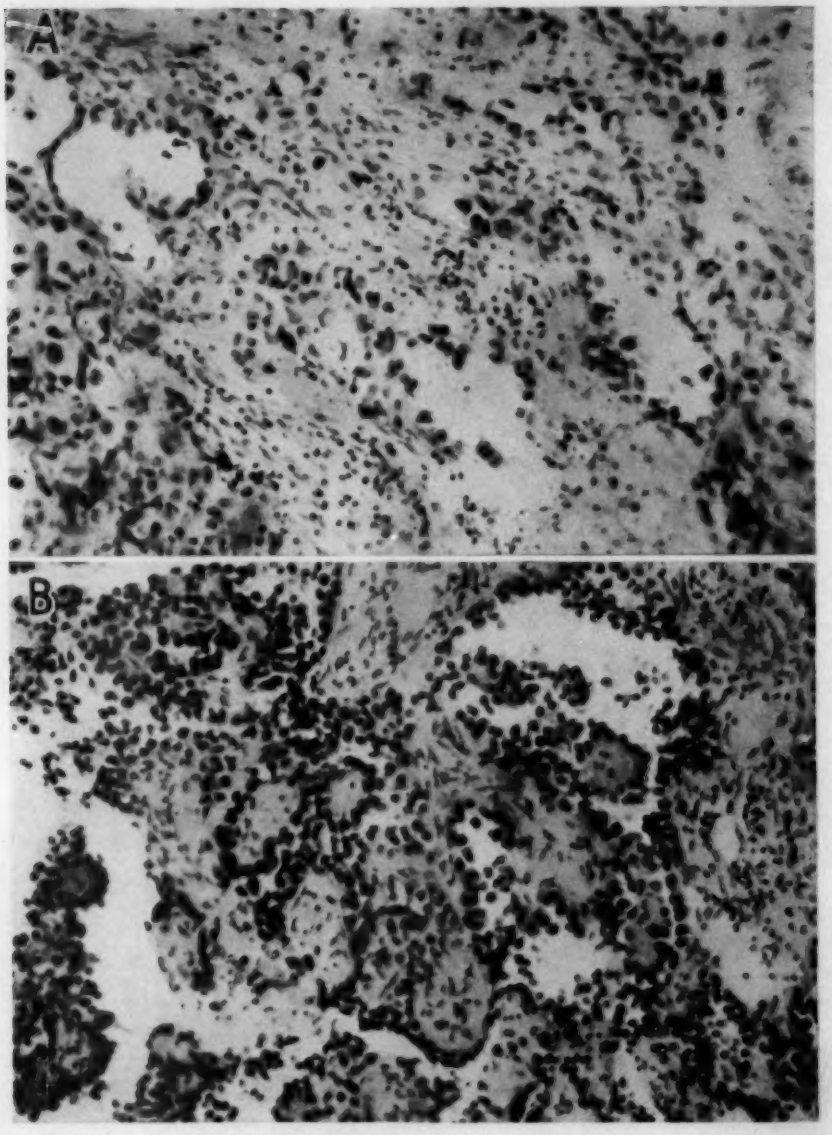

Fig. 2.—Low power photomicrographs. In *A* the malignant character of the growth is indicated by the presence of tumor cells in the stroma (case 5). *B* is taken from a papillary area. The general configuration is similar to that of the more common papillary serous cystadenoma of the ovary, but the characteristic cell indicates a diagnosis of mesonephroma (case 10).

Microscopically, a typical area, which is usually taken from a solid portion of the tumor, is composed of numerous small cystic spaces, characteristically lined by a single layer of epithelium. These cells are usually flat, often broader than they are high, and have bulging nuclei and very scanty cytoplasm (fig. 1 *A*). There are several variations from this picture. In some areas the cells are more proliferative so that the cystic space may be almost filled (fig. 1 *B*). In other areas, in the more malignant cases, cells are found to be growing free in the connective

Ovarian Tumors Described by Authors

Case	Age of Patient	Involvement	Treatment	Result
1	..	Left ovary	Hysterectomy, bilateral salpingo-oophorectomy	
2	43	Both ovaries, peritoneum	Hysterectomy, bilateral salpingo-oophorectomy	Patient died
3	43	Right ovary, peritoneum	Bilateral salpingo-oophorectomy	Patient died within 2½ years
4	55	Left ovary	Hysterectomy, bilateral salpingo-oophorectomy	
5	63	Left ovary	Hysterectomy, bilateral salpingo-oophorectomy	Patient died within 1 year
6	53	Right ovary, peritoneum	Hysterectomy, bilateral salpingo-oophorectomy	Patient died
7	44	Left ovary, peritoneum	Hysterectomy, bilateral salpingo-oophorectomy	Patient died
8	40	Right ovary	.....	Patient died after operation
9	40	Both ovaries, peritoneum	Hysterectomy, bilateral salpingo-oophorectomy, roentgen irradiation	Patient died within 1 year
10*	54	Right ovary	Hysterectomy, right salpingo-oophorectomy	Patient well for 11 years
11*	63	Right ovary	Right salpingo-oophorectomy	Patient died within 3 months
12*	41	Right ovary	Right salpingo-oophorectomy, irradiation with teleradium	Patient well for 11 years
13*	45	Right overy	Hysterectomy, bilateral salpingo-oophorectomy	Patient well for 9 years
14*	72	Both ovaries, peritoneum	Bilateral salpingo-oophorectomy	Patient died within 2½ years
15*	58	Left ovary	Bilateral salpingo-oophorectomy	Patient died within 6 months

* This case was reported in a previous article.[2]

tissue stroma (fig. 2 *A*). In the more cystic areas, where there are papillary projections, examination shows the general configuration of an ordinary papillary cystadenoma of the ovary except for the characteristic cells exhibiting the typical projecting nuclei and scanty cytoplasm (fig. 2 *B*). Sections from a more solid portion of a tumor of this kind show the characteristic multiple spaces previously described.

The connective tissue of mesonephroma is characterized by collagenous fibers and relatively few spindle-shaped cells. Hyalinized areas commonly have an almost cartilaginous appearance (fig. 3).

Here again there may be considerable variation, with other areas showing a rather cellular structure. However, this is unusual, and the sparsely cellular tissue is characteristic.

CLINICAL ASPECTS

Mesonephroma gives rise to symptoms only because of the space and position which it occupies. In this respect it differs in no way from most tumors of the ovary. In no case in this series has there been an associated irregularity of menstruation or any postmenopausal bleeding.

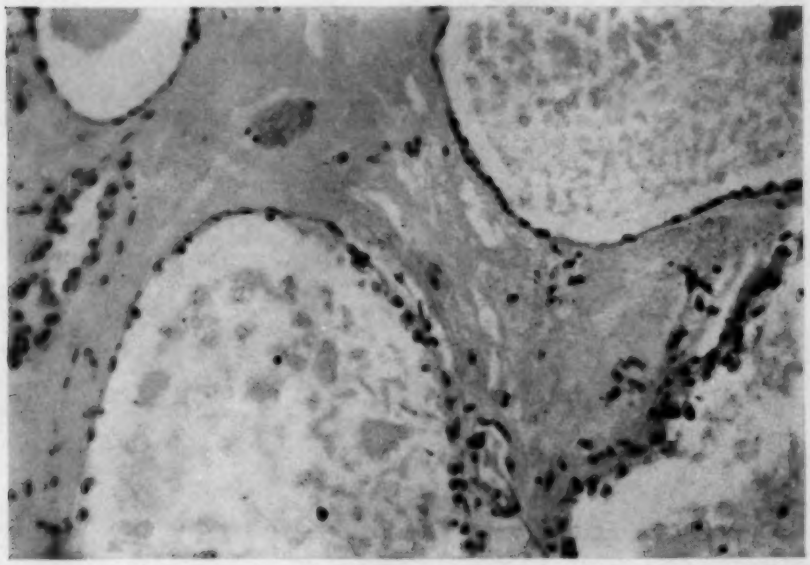

Fig. 3.—Low power photomicrograph. The marked hyalinization of the stroma illustrated in this figure is very characteristic of mesonephroma (case 6).

In those cases in which endometrium was available for study, it was completely atrophic if the tumor was postmenopausal and appeared normal when the tumor occurred before the menopause.

The age incidence is interesting. For the entire group of 15 patients the average age was 51, with extremes of 40 and 72 years.

Follow-up studies on 13 of the 15 patients are available. One died at operation, and 9 died within two and one-half years. Only 3 are living, 1 of them by virtue of radiation therapy. In the 2 cases in which cure was by operation alone, the operative specimen contained little solid tissue, and the tumor could not be distinguished grossly from a papillary serous cyst of the ovary.

THERAPY

Mesonephroma must be considered a malignant tumor. The bilateral occurrence indicates that removal of both ovaries, together with hysterectomy and bilateral salpingectomy, is the method of choice. In many cases the tumor is inoperable when first seen, and recurrences are frequent. In such cases radiation therapy is to be highly recommended. Further experience may prove that the mesonephroma is more sensitive to radiation than other types of malignant ovarian tumors. This possibility is indicated by our experience with a patient who was operated on March 3, 1930. At the time of operation the right ovary measured 15 cm. in diameter, but it was freely movable and easily excised after the pedicle had been clamped and tied. There was a prompt recurrence, and by June 30 a hard mass reaching to within 4 cm. of the umbilicus was palpable. The region of the tumor was heavily irradiated with teleradium, and the response was so favorable that toward the end of 1931 the mass was thought to be operable. She received through two portals a total of 37 gram hours, at 3 inch (7.5 cm.) distance, with a 2 mm. brass filter, the 4 Gm. pack being used. On November 23 exploratory laparotomy showed the tumor to be still inoperable, with extension to the peritoneum. Biopsy at this time revealed that the neoplasm was identical with the original tumor. Further irradiation of the growth was carried out, with the result that the pelvic mass disappeared. During this series she received a total of 3,300 r through three portals, (200 kilovolts; 30 milliamperes; 1 mm. copper and 1 mm. aluminum filter); 50 cm. skin-target distance; 20 × 20 cm. portals. This patient is now apparently free from tumor, eleven years after the recurrence. Only one other patient has had radiation treatment. She was first operated on Sept. 7, 1937, and by April 1938 the tumor had recurred extensively. At that time she was given roentgen radiation through four pelvic portals (264 kilovolts; 30 milliamperes; 1 mm. copper and 1 mm. aluminum filter, 50 cm. skin-target distance; 15 by 15 cm. portals). She received 1,500 roentgens per portal. There was a temporary improvement, but the patient died on Nov. 12, 1938 with the signs and symptoms of intestinal obstruction.

In view of these observations we should certainly advise prophylactic irradiation of the site after removal of a tumor which on histologic examination proved to be mesonephroma. This is advisable because of the otherwise bad prognosis.

HISTOGENESIS

Schiller felt that mesonephroma is derived from mesonephric rests which become included in the adult ovary. His principal reasons for believing this were as follows: The cells have a close morphologic relation to the endothelial-like cells of glomerulus. Isolated structural

units which resemble glomeruli are found in the tumor. Tubules are sometimes present, which may represent carcinomatous degeneration of mesonephric tubules. The tumor may occur in the broad ligament, where the wolffian remains are known to be located. In the embryo the mesonephric glomeruli are closely related to the genital ridge, so that it might be mechanically easy to have a mesonephric rest in the adult gonad.

There are certain objections to accepting this point of view. The morphologic resemblance of the tumor cells to the cells of a mesonephric glomerulus in a 15 to 16 mm. human embryo, though present, is not striking. Furthermore, it is difficult to recognize structural units that bear any great resemblance to glomeruli. We have identified the areas described by Schiller but have thought them of no special significance. They do represent areas of marked proliferative tendency on the part of the tumor cells. Accompanying this proliferation there is an ingrowth of blood vessels within the small cystic spaces, but these are certainly not recognizable as the blood vessels in a glomerular tuft.

On wax reconstruction Schiller felt that the resemblance to glomeruli was striking. However, Kazancigil, Laqueur and Ladewig [3] made a wax reconstruction of a similar tumor but could find no resemblance to glomeruli. According to the latter authors, the apparent structural units were due to the fortuitous direction of the section in relation to the blood vessel within the suspected glomeruli tuft.

Furthermore, no one has demonstrated mesonephric rests in an adult ovary. Such a demonstration would greatly strengthen the possibility of the mesonephric origin of some ovarian tumor. Granulosa cell tumors, for example, are thought by Robert Myer and others to arise from undifferentiated embryonic granulosa cells. This hypothesis is greatly strengthened by the numerous demonstrations of such cells in the hilus of the adult human ovary.

However, one must admit that the histogenetic hypothesis of Schiller is within the realm of possibility. It is inadvisable to be dogmatic in a discussion of histogenesis. The task of determining the histogenesis of large tumors with the methods now at hand seems hopeless. It is nevertheless praiseworthy to attempt this determination. Small tumors, for example those accidentally discovered, are often much more satisfactory for a study of histogenesis.

COMMENT

The position of mesonephroma in the scheme of ovarian nepolasms is still uncertain. There are two important questions; First, is there a pathologic entity such as that described by Schiller and, second, if so, what is the evidence for its histogenesis?

3. Kazancigil, T. R.; Laqueur, W., and Ladewig, P.: Am. J. Cancer **40**:199, 1940.

The evidence at hand, confirmed by our observations, lead us to believe that there is a group of tumors with distinguishing pathologic features requiring their separate classification. It is well to point out that there is some variation in appearance within the group. The tumors described by Kazancigil, Laqueur and Ladewig were embryonic and closely related to the tumors in cases 4, 9 and 10 of Schiller. The tumors in Schiller's cases 5 and 6 were somewhat more differentiated and more nearly related to the 6 original tumors which we described. In an attempt to clarify the status of mesonephroma we have included in the present study only well differentiated tumors and have excluded a greater number because of their borderline character.

The problem of histogenesis is complex. Schiller's evidence for the mesonephric origin has been summarized. Kazancigil, Laqueur and Ladewig, on the other hand, denied the epithelial origin and held that the tumors were angioendotheliomatous in derivation. They reported finding numerous areas of blood formation in one of their tumors. Their interpretation is based on morphologic grounds and on their failure to confirm Schiller's finding of glomerular-like structures. They proposed the name papilloendothelioma ovarii.

In our opinion it is likely that both of these points of view need revision. It seems to us possible that Kazancigil, Laqueur and Ladewig favored an endothelial origin because they had the opportunity to observe only the most undifferentiated tumors within this group. If an angioendothelial origin is correct, the absence of such tumors in organs other than the ovary must be satisfactorily explained.

Our own impression is that the tumors are epithelial in origin, of a definite pathologic unity and of an unknown histogenesis.

SUMMARY

We have added 9 new cases of mesonephroma and summarized the clinical and pathologic features of 15 cases of mesonephroma of the ovary. There is little doubt that mesonephroma is a pathologic entity. Whether or not its recognition will prove of value from a therapeutic or a prognostic aspect remains to be determined. Of 2 tumors in the present series treated with radiation, one responded remarkably, and the patient is now living and well eleven years after a recurrence of her original growth.

The histogenesis of mesonephroma seems to us to be still uncertain. However, the mesonephric origin ascribed to them by Schiller is plausible and should be retained unless more conclusive evidence to the contrary is forthcoming.

ABSTRACT OF DISCUSSION

DR. WALTER SCHILLER, Chicago: About ten years ago, after I had had the opportunity of examining a great number of cystic tumors of the ovary, I made the suggestion that a small group of tumors represents an entity and should be

separated from the others for the morphologic reason that this type of tumor shows as a covering of the cystic cavities not epithelium but endothelium with low, flat or mushroom-shaped cells, most of which are arranged in such a way that one cell is not in contact with the two neighboring cells. These tumors may form solid masses presenting a mesenchymatous structure which is entirely different from the epithelial structure of carcinoma.

In the slide one sees here a solid part of a malignant mesonephroma which represents this type of solid structure, in which each cell is connected with the neighboring cells by fibrous projections, entirely different from the solid epithelial masses formed by the carcinomatous, cystic papilloma.

A more difficult and more complicated matter is to prove the second part of my suggestion—to trace such tumors back to the mesonephros. Most important for this histogenetic explanation seems the presence of a characteristic structural unit, which is found in great numbers in some of these tumors, is represented only by a single unit in the majority, and is entirely missing in some. This structural unit is definitely characteristic and specific. I have examined many other ovarian tumors and tumors of other organs and was not able to find this structural unit. This unit is represented by small cavities, each of which contains only one relatively large papillary projection, and this papillary projection contains one tuft, one loop of a capillary, and this tuft is lined, and similarly the cystic cavity is lined, with an endothelium-like covering, which in certain of these units shows at the tufts a higher, more columnar type of cell.

This unit is duplicated by one structure only, and that is the fetal glomerulus. This shows in its early phases high columnar epithelium, which later is brought down and which finally, during the first or second year after birth, assumes the endothelial structure.

In this slide is a mesonephroma of a young girl. It is composed of a great number of these units, little cavities, each cavity containing one papillary projection, and this containing one capillary, which is lined with endothelium duplicating the lining of the fetal glomerulus.

In this slide is a mesonephroma of an adult woman. It shows the same unit, the same capillary tuft. The lining here is a little higher, more of the fetal type.

This is a diagrammatic drawing. You see the mesonephroma (*a*), the ordinary papilloma (*b*) and the perithelioma (*c*). In *a* is a little cavity, in *b* a large cavity; in *a* one papillomatous projection, in *b* numerous projections; in *a* a small amount of connective tissue and a relatively large capillary tuft, in *b* a large amount of connective tissue and a few capillaries which are very small compared with the large masses of connective tissue. In *c* there is the peritheliomatous proliferation of the perithelium, but no cystic cavity can be found.

The slides show clearly the morphologic difference between the unit of the mesonephroma and the structure of the papilloma and the structure of the perithelioma.

Since my first paper, I have been able to secure one more case, which may give further evidence of the renal origin of this unit. Dr. Tracy Mallory, of Boston, supplied the slides and the history of this interesting case. The patient was a 52 year old man who was admitted to the hospital with hematuria. At operation a tumor, 2.5 by 3 cm., was found at the pelvis of the right kidney. It was a cystic adenoma, the cells of which partially duplicated the tubular cells of the kidney.

In this slide are areas more cystic and other areas more tubular. These tubular parts are in direct connection with the normal tubular cells of the kidney, and, in addition to that, this section shows parts which duplicate the glomerular struc-

ture of the mesonephroma. There is one projection in a small cavity, containing one tuft with little connective tissue, this occurring only between the endothelial covering and the capillary.

In this slide is the same structure, one little cystic cavity, one capillary tuft covered with endothelium, the same type which lines the cystic cavity.

The similarity between this renal tumor and the ovarian mesonephroma is striking.

Dr. Emil Novak, Baltimore: Not only has Dr. Jones given, in addition to the study of his own cases, a review of the still meager literature on this subject, but he has evaluated conservatively the problem of the histogenesis of these tumors. A sifting out from the hodgepodge of malignant epithelial tumors of the ovary has already yielded the recognition of certain special types, such as the Krukenberg growths and, in more recent years, such special tumors as granulosa cell carcinoma, arrhenoblastoma, dysgerminoma and the Brenner tumor.

While Dr. Schiller has offered evidence pointing to a mesonephric origin, it cannot be said that such a histogenesis is yet clearly established. Among the features which have been emphasized are the character of the epithelium and the tubular pattern. It is true that the epithelium resembles the mesonephric type, but a similar type is seen in ovarian growths which quite certainly have their origin in the germinal epithelium. One sees it not infrequently, for example, in serous cystadenoma of the ovary and in the malignant prototypes of that tumor. As a matter of fact, tumors arising from the germinal epithelium rather characteristically show a tendency to polymorphism of the epithelial constituents. In the tumors described by Dr. Jones, who was good enough to let me see his original sections, neither the cell type nor the tubular pattern are by any means found throughout the sections.

As to the question of glomerulus formation, I have not encountered pictures which, on histologic examination at least, could not be explained more easily on the basis of tuftlike epithelial proliferation or the angle of section of tortuous tubules. The reconstruction studies of Schiller, as Dr. Jones has indicated, have not as yet been supported by other investigators.

The term "mesonephroma" commits one at once to the concept of a mesonephric origin of these tumors, an explanation which may or may not prove to be correct. Perhaps it might have been more cautious had Dr. Schiller entitled his original paper not "Mesonephroma of the Ovary" but "The Possible Mesonephric Origin of Certain Ovarian Tumors."

Dr. Walter Schiller, Chicago: I should like to add that I have had the opportunity since I published my paper to examine numerous slides of ovarian tumors diagnosed as papilloma and papillary cystoma, and never have I found a transformation of the epithelium into a true endothelial lining.

Dr. Howard T. Karsner, Cleveland: This whole matter is one of great interest. I have nothing to contribute directly to the discussion, but in some recent studies of ovarian tumors my associates and I have been astonished to learn how much information can be obtained from special stains. In connection with many of these lesions we have depended too greatly on morphologic appearances and on the hematoxylin and eosin stain. We have learned a great deal by the use of the mucicarmine stain. In the study of all tumors of this general category particular attention should be paid to special staining methods.

OXYURIASIS AND APPENDICITIS

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AND
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ROTTERDAM, NETHERLANDS

A connection between the presence of Oxyuris and the occurrence of appendicitis has been suspected for a long time (Brumpt [1]). The extensive and systematic work of Rheindorf [2] reawakened interest in the problem. Rheindorf expressed the opinion that acute inflammation of the appendix may result from the direct activity of the threadworms; Rheinhardt and Läwen,[3] Goldzieher,[4] Noack,[5] Riff [6] and Ssolowjew [7] came to similar conclusions. Others (e. g., Kaufmann [8]) have believed that the production of appendicitis by threadworms has not been proved. Askanazy,[9] Becker,[10] Christeller and Meyer,[11] Staemmler [12] and Gordon [13] disagreed in part, while Aschoff [14] and his pupils Hueck [15] and Brauch [16] disagreed completely with the conclusions of Rheindorf. Brauch concluded that all the lesions which Rheindorf considered specific for the activity of Oxyuris were artefacts resulting from manipulation, fixation or embedding of the appendix.

From the Pathological Anatomical Laboratory of the Municipality Hospital.

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11. Christeller and Mayer, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, pt. 3, p. 507.
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14. Aschoff, L.: Berl. klin. Wchnschr. **57**:1041, 1920.
15. Hueck, O.: Frankfurt Ztschr. f. Path. **13**:434, 1913.
16. Brauch, M.: Beitr. z. path. Anat u. z. allg. Path. **71**:207, 1922-1923.

The purpose of this paper is to provide evidence that may help in deciding whether Oxyuris vermicular, a parasite of wide distribution among young people, can cause lesions in the appendix which form portals of entry for microbes.

Aschoff,[17] who found oxyurids only twice in his first series of 1,000 appendixes, demonstrated the high incidence of the worms in surgical specimens. Subsequently, he confirmed many of Rheindorf's findings but did not accept the latter's conclusions. Aschoff [18] felt that oxyurids cause a disease which he called appendicopathia oxyurica and which resembles appendicitis clinically, though the attack is atypical.

Aschoff gave an excellent description of the primary inflammatory lesion in appendicitis. It arises in a recess of the appendical mucosa, is often multiple and usually appears as a wedge-shaped focus of acute inflammation pointing to the lumen; on the surface there is a small epithelial defect covered by threads of fibrin and leukocytes. Several primary foci may coalesce and give rise to phlegmonous inflammation.

The genesis of appendicitis is still unknown. At present the hematogenous route is no longer considered likely, and it is assumed that small injuries of the mucosa form a portal of entry for intestinal microorganisms. It is believed that oxyurids frequently injure the mucous membrane, and it is possible that these erosions may become secondarily infected.

Oxyurids are found in about 30 per cent of all appendixes examined —sometimes a hundred or more in a surgical specimen. The worm has a transversely striated cuticle, which forms two ridges along the ventral and dorsal surfaces. It is very motile and is able to attach itself firmly to the intestinal mucosa by the bulbus pharyngealis. In the pregnant female worm, the uterus is filled with eggs to such an extent that the activity of the bulbus pharyngealis is interfered with, and the worm drops into the lumen of the intestine to be carried away. The male is able to remain attached throughout life (Koch [19]; Brumpt [1]).

METHODS

In order to study large areas of the appendical wall, we examined only longitudinal sections. At first after fixation in a solution of formaldehyde, the appendix was incised and the halves embedded in paraffin. Later, in more than half of our cases the specimen was embedded without being opened. This was done to keep the contents intact. For purposes of better fixation, the tip of the appendix was cut off and fixed separately. Very long appendixes were cut in two. The block or blocks were cut in the microtome until the lumen appeared in the sections,

17. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908.

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and two preparations were stained. When an oxyurid was found, a series was cut and every tenth section stained. Seldom was a long series necessary in order to find definite lesions associated with the worm. Only rarely were lesions absent.

It was not our aim to determine how often oxyurids occur; hence we selected for a detailed study only those specimens in which the worms were easily detected.

OBSERVATIONS

Appendixes Showing Oxyurids But No Inflammation and No Changes in the Mucosa.—Only 8 of our 36 specimens belonged in this group. Five appendixes showed signs of chronic inflammation. The mucosa contained a moderate number of eosinophils in 5 and a large number of these cells in 3. The lymphatic vessels of the serosa contained a few lymphocytes in 4 and an appreciable number of these cells in 2. One sectioned appendix contained fifteen transverse sections of the worms; the remaining 7 contained five or less. Fecal concretions occurred in 3, and a small quantity of blood was seen in the lumens of 2.

Figure 1 *A* demonstrates the care used in determining the degree of injury caused by an oxyurid. Here erosion of the epithelium with underlying necrosis is seen in close approximation to the transverse section of the worm. We considered this finding negative, since in serial sections the relation of the lesion to the parasite did not seem conclusive.

Appendixes Showing Typical Lesions of the Mucosa.—Typical lesions were found in 22 of our 36 appendixes. Often the oxyurids made half-moon-shaped impressions in the epithelium on which they lay. Usually these were found in the narrow recesses of the mucosa, less often in other places. These impressions often showed a deeper indentation at the spot where the cuticular ridge had pressed on the epithelium. According to Brauch,[16] such impressions are caused exclusively by pressure of the column of feces which, after hardening, presses the worm into the wall, but we were able to follow the beak-shaped imprint in serial sections and saw these impressions also in appendixes which were practically free of feces. Contrary to the description of Brauch, the epithelium was generally flattened and atrophic and in the deepest places almost endothelial-like. At the edges the cells became tall and slender and stained red with acid dye (fig. 1 *B*). In the region of the impression a few epithelial cells might be wanting, and small erosions and areas of necrosis were seen (fig. 1 *C*).

In evaluating these defects, we looked for signs of a vital reaction. Since hemorrhage may be caused during operation, we considered an inflammatory reaction the only evidence of a vital reaction. Threads of fibrin with varying numbers of polymorphonuclear leukocytes, lymphocytes, erythrocytes and mucus could often be seen on these defects. This reaction did not differ from that observed by Aschoff in appen-

Fig. 1.—*A*, mucosal changes independent of the oxyurid in the neighborhood. × 75. *B*, impression made by an oxyurid. At the edge the epithelium is deformed. × 340. *C*, necrosis of the mucosa and deposition of fibrin. × 230. *D*, oxyurids in recesses of the mucosa, penetrating into the glands. × 45.

dicitis. We ruled out by our serial sections the possibility that these changes were incidental to an unrelated "primary" appendicitis. Sometimes these threads were multiple. When the oxyurid was a little bent and the head and the tail were not connected, the thread could be seen to continue from one part of the body to the other. If the worm had changed its place a little, the thread attached to it was dragged behind like the tail of a comet. The thread sometimes proceeded far into the lumen.

Occasionally the oxyurids penetrated into the glands, where they were found deep in the recesses of the appendical mucosa (fig. 1 *D*). The lumens dilated, and the epithelium underwent changes similar to those just described. In some instances irregular defects in the glandular epithelium occurred, beneath which hemorrhage and inflammatory exudate were found (fig. 2).

These typical lesions, as stated, were found in 22 of 36 appendixes studied. The age distribution was as follows: under 5 years, 9; from 5 to 10 years, 2; from 10 to 25 years, 7; approximately 60 years, 2; and 70 years or over, 2. In only 3 appendixes were eosinophils seen in small numbers; they were numerous in 15 and very abundant in 4. Blood was seen within the lumens of 10 appendixes, lymphocytes in 12, pus in 7 and a fecal stone in 5. In 7 appendixes we found scars of old inflammation with partial obliterations of the lumens of 3. Other lesions will be described in the following sections.

Encapsulated Oxyurids.—Two appendixes had worms encapsulated in their walls. In one the worm was lying in an old abscess, surrounded by a coating of epithelial cells and fibroblasts; the neighboring tissue was infiltrated by eosinophils (fig. 2 *B*). In the other, two nodules resembling tubercles were seen. These were composed of a central area of polymorphonuclear leukocytes surrounded by epithelioid and giant cells. In other sections these nodules were found to coalesce and to contain a dead oxyurid, which was slightly calcified.

In 4 other specimens nodules similar in size and form were found. In one nodule, part of a worm was seen; the remaining three contained no recognizable oxyurids, but oxyurids were found in the appendical lumens. Only one transverse section of a worm was seen in the one nodule, while in two others the worms were not seen in more than sixty sections. In the fourth nodule no worms were present, but numerous oxyurid eggs were seen in the inflamed appendix (fig. 3 *B*).

Specimens Showing Ulcerative Appendicitis or Acute or Subacute Periappendicitis Associated with the Presence of Oxyurids.—In 19 of the 36 specimens, suppurative changes occurred. These included the 5 already described in which calcified nodules were found. Of these, 2 showed a moderately broadened serosa infiltrated with polymorphonuclear leukocytes, among which eosinophils were outstanding. A third,

with ulcerating phlegmonous inflammation, contained oxyurid eggs. The fourth appendix was characterized by empyema of the distal portion, while the fifth showed large numbers of eosinophils within its lumen. It

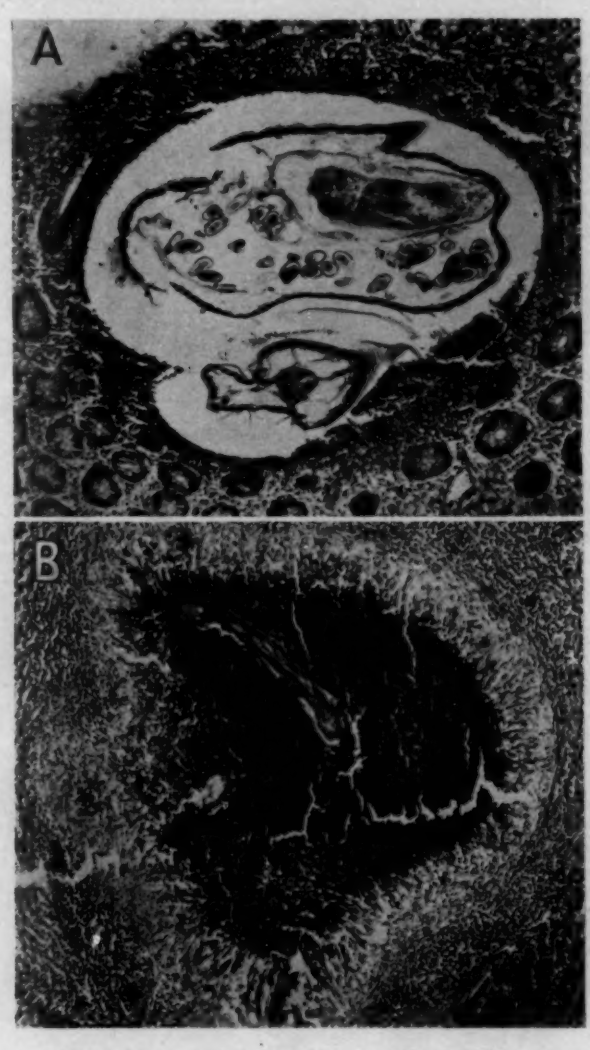

Fig. 2.—*A*, inflammatory reaction about an oxyurid which has penetrated into the mucosa. × 75. *B*, reaction about oxyurids in a chronic abscess. × 75.

seems probable that at least part of these inflammatory changes were associated with the encapsulated worms.

In 14 other specimens the inflammatory changes were as follows: 8 showed acute or subacute periappendicitis; 2, empyema of the appendix; 1, purulent phlegmonous appendicitis; 1, localized inflamma-

tion with ulceration. In 1 appendix there was evidence of an old perforation with encapsulated foreign bodies in the serosa.

As it is impossible to show a connection between the inflammation and the presence of the oxyurids in the lumen (as Ehlers [20] could in his case), we content ourselves with a simple statement of our findings.

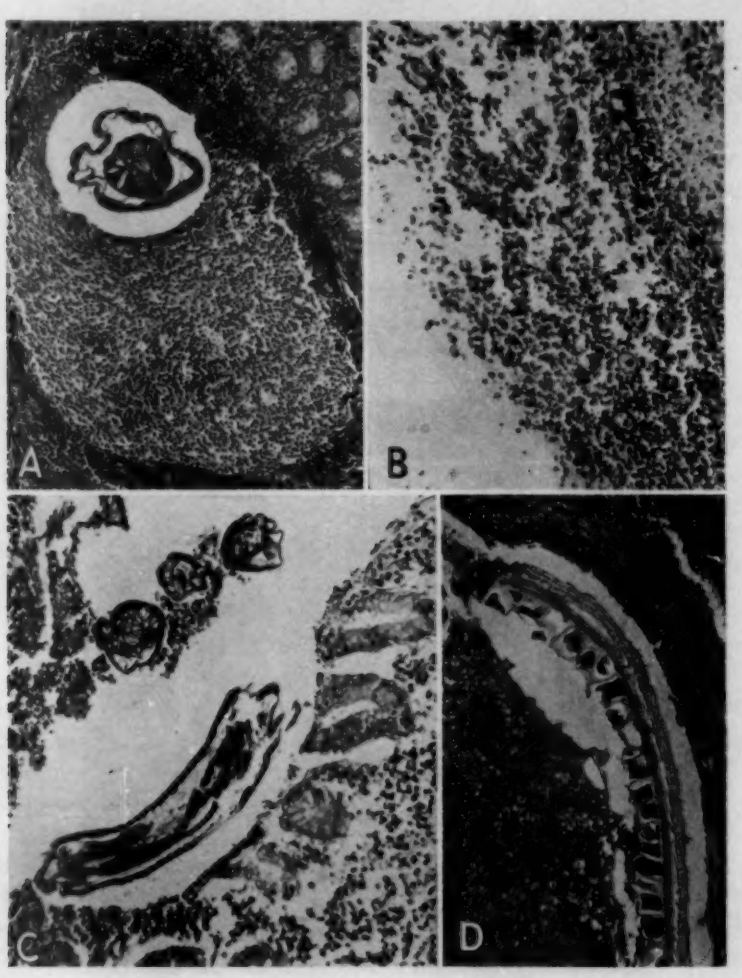

Fig. 3.—*A*, immigration of a worm into a lymph follicle without inflammation. × 75. *B*, appendicitis with ulceration. Note oxyurid eggs in the purulent exudate. × 100. *C*, impression made in the mucosa by the worm, with inflammation. × 125. *D*, phlegmonous appendicitis with kernel of wheat from brown bread. × 80.

Postvital Immigration of Oxyurids.—Most authors describe the oxyurids in the follicular apparatus and in other places in the mucosa

20. Ehlers, H. W. E.: Deutsche Ztschr. f. Chir. **213**:275, 1929.

as lying in round smooth-walled spaces about which no tissue response is seen. This is not a rare condition and occurred in 5 specimens of our series. Figure 3 *A* shows such a reactionless immigration. Gordon was the first to point out that this is a postvital reaction, the immigration having occurred after the appendix was resected. We saw conclusive proof of this phenomenon in 1 specimen, in which the oxyurid perforated the tip of the appendix without any inflammatory reaction. Inflammation develops rapidly when perforation occurs during life.

COMMENT

The immigration of the oxyurid into the wall of the appendix without inflammatory reaction is one of the principal arguments in favor of the worm's harmlessness. Our observations support the opinion of Gordon, who considered this a postvital process. They indicate that immigration of the worm causes a reaction similar to that produced by any other foreign body.

Appendixes containing oxyurids often show signs of purulent inflammation. The most characteristic lesions caused by the oxyurids are those described as half-moon-shaped impressions with atrophy and necrosis of the epithelium, erosion and necrosis in the mucosa and inflammatory exudation usually consisting of fibrin, leukocytes and mucus.

Most authors agree that oxyurids may cause lesions as here described, although Gordon, who has studied 26,000 appendixes, considers such lesions exceptional. In our small series of 36 specimens in which the oxyurids were found, the lesions were absent in only 8.

Can the lesions produced by the oxyurid form the portal of entry for bacteria and lead to true appendicitis? The localization of the lesion associated with the worm is the same as that of the primary inflammatory lesion described by Aschoff. This lesion is found most often in a recess of the appendix and is usually multiple. A superficial fibrin thread is found in both; both are found in young persons. Our study included 5 patients under 10 years of age, 13 between 10 and 20, 13 between 20 and 30 and 3 over 30 years of age.

The fact that in Aschoff's primary lesion a connection with an oxyurid can so seldom be shown is not sufficient reason to deny such an association. If one considers the great mobility of the worm, it is not surprising to find that it is distant from the lesion of infection. Hueck described a case as follows:

> . . . in one place close to a spot denuded of epithelium, lies the transverse section of a parasite, apparently an oxyuris. It is surrounded by purulent matter. In the mucous membrane severe injury is noticeable. . . . The presence of the parasite in a typical primary lesion may be accidental.

In Goldzieher's case 150 phlegmonous appendicitis was caused by oxyurids. Rheinhardt and Läwen reported 2 and Rheindorf several

examples of similar lesions. We have observed ulcerative appendicitis with oxyurid eggs in the pus. The following are descriptions of this case and of another somewhat uncommon case which illustrates the changes here discussed.

CASE 1.—In an appendix distended with thin pus there were ulceration and phlegmonous inflammation with many eosinophils in the outer layers of the wall of the appendix. Throughout the wall, particularly in the ulcerated parts of the mucosa, numerous nodules of foreign body granulation tissue were found. Most of these contained eosinophilic leukocytes, epithelioid cells and bizarre epithelial giant cells. In the distal end of the appendix the dilated glands gave rise to small cysts filled with mucus and leukocytes. In the pus (fig. 3 *B*) and in the granulomas many oxyurid eggs were seen. The worm itself was not found. In the wall a tuberculoid structure containing a calcified worm and a more recent granuloma with part of a worm were noted.

CASE 2.—A few centimeters from the tip of the appendix a carcinoid, 7 cm. in diameter, was seen infiltrating the wall and obliterating the lumen. Beyond this there was a mucocele, 1 cm. in its greatest diameter. In this region the mucosa did not show any inflammatory reaction, but there was a localized subacute purulent periappendicitis in the serosa overlying the mucocele. In the distorted lumen of the appendix near the tumor, about ten transverse sections of oxyurids were found lying in characteristic impressions, causing slanting of epithelium and erosion (fig. 3 *C*). In some follicles postmortem reactionless migration was found. In examinations of a great number of sections, no connection was seen between oxyurid defects and periappendicitis. In the first case the inflammatory changes could be attributed to the presence of oxyurids; in the second, the tumor may be held responsible for the peritoneal reaction.

CASE 3.—The appendix showed localized ulcerative and phlegmonous inflammation. Transverse folds of mucosa and submucosa divided the lumen into small cavities connected by narrow slits. In one of these was found a foreign body: the cuticle of a grain of corn such as is found in brown bread. This was embedded in purulent granulation tissue (fig. 3 *D*).

The position of the foreign body in this case and the absence of feces suggest that the suppuration was secondary to the local lesion caused by the foreign body. Similar foreign bodies are common in the lumens of inflamed and normal appendixes.

SUMMARY

In Holland Oxyuris vermicularis is found frequently in appendixes, especially those of young people, and gives rise to characteristic lesions in the mucosa. When the parasite penetrates the deeper strata of the appendical wall, it causes a foreign body reaction and abscess formation; encapsulation and calcification may follow. Oxyuris may be a primary cause of appendicitis. Postmortem migration of the worm causes no reaction (Gordon).

THE HEART IN COMBINED SYPHILITIC AORTIC VALVULITIS AND RHEUMATIC HEART DISEASE

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The effect on the heart of syphilis and rheumatic fever occurring together has received little attention. Most of the monographs on heart disease and the standard textbooks of pathology give it but few words or ignore it completely.[1] At City Hospital, Welfare Island, New York, it has been encountered frequently in the wards and observed on several occasions at necropsy. The present study is based on 14 cases in which the patients were under observation for a sufficient length of time to enable us to obtain complete clinical data and in which at necropsy the aortic valve was found affected by syphilis. It includes 5 cases which formed part of a previous report.[2]

The coexistence of syphilitic and rheumatic infections has been noted in cases of heart disease by few observers. Cowan and Rennie [3] in a study of 104 patients with disease of the aortic valve found evidence of syphilis in 32, among whom 3.1 per cent had lesions of the mitral valve. Among an equal number with mitral disease, 0.8 per cent had evidence of syphilis. In a group of rheumatic children Fordyce [4] found 9 whose progress was less satisfactory than is usual for such patients.

From the Pathological Laboratory, City Hospital, Welfare Island, Department of Hospitals.

1. White, P. D.: Heart Disease, New York, The Macmillan Company, 1935, p. 365. Lewis, J.: Diseases of the Heart, ed. 2, New York, The Macmillan Company, 1937. Mackenzie, J.: Diseases of the Heart, ed. 3, London, Oxford University Press, 1918. Fishberg, A. M.: Heart Failure, ed. 2, Philadelphia, Lea & Febiger, 1940. Levine, S. A.: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, 1936. Boyd, W.: A Text-Book of Pathology, ed. 3, Philadelphia, Lea & Febiger, 1938. MacCallum, W. G.: A Text-Book of Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1924.

2. Lisa, J. R., and Chandlee, G. J.: Arch. Int. Med. **54**:952, 1934.

3. Cowan, J., and Rennie, J. K.: Brit. M. J. **2**:184, 1921.

4. Fordyce, A. D.: Brit. M. J. **1**:530, 1930.

Investigation disclosed evidence of congenital syphilis. Buday [5] found 10 instances of syphilis and chronic fibrotic valvulitis among 937 autopsies on patients dead of endocarditis at the University of Budapest, in Hungary. In the autopsy material of Vanderbilt Hospital, Nashville, Tenn., Swanson [6] found rheumatic heart disease in 4 of 57 instances of cardiovascular syphilis, an incidence of 7 per cent.

Cases with acceptable gross and microscopic evidence of syphilitic aortic valvulitis and rheumatic heart disease are scanty. The first report appears to be one from the Massachusetts General Hospital, in Boston.[7] The patient was a man 40 years of age with syphilitic aortitis, commissural syphilis of the valve, mild chronic rheumatic mitral valvulitis and acute rheumatic panvalvulitis and myocarditis. Sager and Sohval [8] reported 3 cases. In 2 there was combined syphilitic and rheumatic aortic valvulitis. In the first case the rheumatic disease also affected the tricuspid and pulmonic valves and the myocardium. In the second case there was chronic rheumatic mitral valvulitis, and both valves were involved by Streptococcus viridans endocarditis. In the third case there were syphilitic aortitis and valvulitis, syphilitic myocarditis and chronic rheumatic valvulitis of the mitral and tricuspid valves. The case of Cossio and Berconsky [9] was one of syphilitic aortitis, commissural syphilis and chronic active rheumatic mitral valvulitis. Swanson [6] reported 2 cases. Aortic and commissural syphilis with inactive rheumatic mitral and tricuspid lesions were present in his case 2. In his case 3 the syphilitic valvulitis resulted in gross deformity and was associated with acute rheumatic myocarditis; the valves were unaffected.

There are a few cases with acceptable gross descriptions but lacking microscopic confirmation. In Stolkind's [10] case the aortic valve was syphilitic and incompetent and the mitral valve stenotic. Swanson in his report described a case which he did not include among the proved cases. Heidenreich, Joselovich and Herbstein [11] described aneurysm of the intrapericardial portion of the aorta, commissural syphilis of the aortic valve and sclerotic vegetations of the posterior mitral leaflet.

More doubt arises in regard to other reports. In 24 autopsies on persons with cardiovascular syphilis Reid [12] found rheumatic heart dis-

5. Buday, L.: Frankfurt. Ztschr. f. Path. **38**:450, 1929.

6. Swanson, H.: Am. Heart J. **18**:672, 1939.

7. Cabot Case 18131, New England J. Med. **206**:689, 1932.

8. Sager, R., and Sohval, A.: Arch. Path. **17**:729, 1934.

9. Cossio, P., and Berconsky, I.: Rev. argent. de cardiol. **2**:37, 1935.

10. Stolkind, E. J.: Brit. J. Child. Dis. **17**:126, 1920.

11. Heidenreich, A. J.; Joselovich, M., and Herbstein, J. M.: Prensa méd. argent. **25**:613, 1938.

12. Reid, W.: Am. Heart J. **6**:91, 1930.

ease in 4. He stated that in 2 cases the presence of rheumatic lesions was definite, in 1 their presence was probable and in 1 there was a combined lesion, but he gave neither gross nor microscopic evidence for his conclusions. A Cabot case report [13] of extensive syphilitic aortitis with a few minute verrucous lesions of the mitral valve and a myocardial lesion is doubtful. Only one questionable Aschoff body was seen, and microscopic observations of the mitral valve were not reported. Another Cabot case report [14] dealt with syphilitic aortitis, commissural syphilis and a valvular and a myocardial lesion interpreted by Mallory as possibly rheumatic.

MATERIAL STUDIED

Among 3,496 consecutive cases in which autopsy was performed at City Hospital between Jan. 1, 1927 and Dec. 31, 1940 there were 311, or 8 per cent, in which gross evidence of syphilis of the aorta or of the aortic valve was found. Rheumatic heart disease was observed in 31, or 10 per cent, of them, found either at the necropsy table or on histologic examination. Of the cases in which rheumatic lesions were observed in the heart, there were 17 in which syphilis was limited to the aorta and did not affect the aortic valve. Syphilitic valvulitis was present in 14. The latter group forms the basis of this report. In each case the clinical syndrome was that of cardiac dysfunction.

METHODS

The method of sectioning the hearts and the stains employed were similar to those reported in another paper.[15] Particular attention was paid to the different portions of the aortic valve. In 1 case only 12 blocks were cut; in the remainder, 36 or more.

The criteria used for the diagnosis of syphilitic valvulitis were those laid down by Saphir and Scott,[16] with which our observations agree. The gross finding was a widening of the commissure. Important findings at the commissure were (*a*) endarteritis of the vasa vasorum, producing usually fibrous endarteritis or more rarely splitting of the elastica, (*b*) perivascular infiltration by lymphoid and plasma cells, (*c*) vascularization of the media by thin-walled vessels surrounded by inflammatory cells and (*d*) hyalinization of the inner part of the media and of the intima. The vascularization of the media was frequently found to extend through almost the entire thickness of the media, and the cellular reaction often had a high component of monocytes. It was also found that the plasma cells in the adventitia were abundant but seldom comprised more than slightly above half the total number of cells. The central portions of the leaflets, if affected by syphilis alone, were mainly fibrotic and avascular.

The diagnosis of rheumatic aortic valvulitis rested on a histologic examination of the bodies of the cusps. The criterion was chronic productive inflammation accompanied by thickening of the arterial walls, which was characterized by delicate elastification of the intima. The lumen was frequently narrow and

13. Cabot Case 16492, New England J. Med. **203**:1163, 1930.
14. Cabot Case 18081, New England J. Med. **206**:401, 1932.
15. Royster, C. L.; Lisa, J. R., and Carroll, J.: Arch. Path., to be published.
16. Saphir, O., and Scott, R. W.: Am. J. Path. **3**:527, 1927.

eccentric. In the study of the commissures, the findings of Gross and Silverman [17] could not be used, principally because of the choice of our material. Only one finding proved of value, the presence of thick-walled arteries similar to those seen in the cusps. Evidences of rheumatic disease in other regions of the heart were those generally accepted.

The ages ranged from 16 to 59 years; 1 patient was in the second decade, 2 in the third, 5 in the fourth and 3 each in the fifth and sixth. The group as a whole was comparatively young; the average age was 38.3 years, and only 3 were older than 50.

The majority were males; there were 11 men and 3 women. In this matter of sex predominance the group resembles one of syphilitic patients with heart disease more closely than any observed group of patients with rheumatic heart disease.

The cases were equally divided among the white and the Negro race. Among the white patients, 5 were men and 2 were women. Among the Negroes, 6 were men and 1 was a woman. The hospital population, however, is predominantly white. On this basis, therefore, the occurrence of the combined infection appeared more frequently among the Negro than among the white patients..

The weights of 13 hearts were recorded; they varied from 400 to 1,050 Gm. In 6 instances a chronically adherent pericardium of rheumatic nature was included. One heart which was not weighed was described as greatly hypertrophied.

The histologic appearance of the myocardial fibers proved a better index of hypertrophy than the weight. Hypertrophy of the left ventricle was marked in 7 hearts, mild in 4 and absent in 3. Right ventricular hypertrophy was marked in 7 hearts, moderate in 5 and absent in 2. The changes in the left auricle usually approximated those in the right ventricle. The right auricle was seldom affected, definite changes being observed in only 2 instances.

The main gross lesion of the commissures was syphilitic, and the more severe degrees of involvement predominated. In 1 heart, 2 of the commissures were slightly widened and 1 was normal. In a second heart the involvement was slight in all. A third heart had one commissure moderately widened and two only slightly. Two hearts had both syphilitic and rheumatic lesions; in each heart two commissures were widened and one had fusion of the leaflets.

Combined syphilitic and rheumatic lesions of the commissures were revealed in 7 cases by histologic examination and were associated with gross and microscopic evidence of rheumatic valvulitis of the bodies of the cusps. Commissural syphilis alone was confirmed in the remaining 7 cases by microscopy. The bodies of the cusps in 2 instances had rheumatic lesions; 1 cusp was syphilitic, 2 were normal, 1 had calcified plaques and 3 acute infectious endocarditis. In 9 of the 14 cases, therefore, the aortic valve was affected by both diseases.

Rheumatic mitral valvulitis was present in all cases. It was found once by histologic examination only. In the other instances it was evident grossly. The lesion was predominantly stenotic in 7, regurgitant in 3 and both regurgitant and stenotic in 2. In 2 cases severe deformity was not produced. Usually the lesion was chronically active; in 1 instance it was very acute and in 4 it was either inactive or completely healed. Three cases were complicated by superimposed acute endocarditis. In the first case there was combined syphilitic and rheumatic disease of the aortic leaflets and commissures and the base of the anterior mitral

17. Gross, L., and Silverman, J.: Am. J. Path. **13**:389, 1937.

leaflet beneath the R-P commissure had a shallow chronic ulcer due to Str. viridans (fig. 1). In the second case an endocarditis due to the hemolytic streptococcus was imposed on uncomplicated syphilis of the aortic valve. An acute bacterial endocarditis, probably pneumococcic, was found in the third case; the patient died of pneumonia due to type 3 pneumococci. Syphilitic mitral valvulitis was present in 1 case; the aortic valve had a severe syphilitic involvement and the base of the anterior leaflet beneath the posterior aortic cusp had a large granulomatous lesion with a pinpoint perforation (fig. 2*A*). Histologically, the lesion consisted of miliary gummas with central necrosis.

Rheumatic valvulitis of the tricuspid leaflets was seen on gross examination in 5 cases. It usually involved the mesial cusp and caused no great deformity of the valve. In 1 case, however, all the leaflets were sufficiently affected to produce an appreciable degree of stenosis. Four additional cases were discovered on histologic examination.

Fig. 1.—Combined syphilitic and rheumatic aortic valvulitis and chronic Streptococcus viridans ulcer of the base of the anterior leaflet of the mitral valve.

The pulmonary valve had rheumatic disease in 4 instances, twice with gross and twice with histologic lesions. A syphilitic involvement of the pulmonic ring by extension from the aorta was found in another case; the cusps themselves were normal.

Syphilis of the aorta encroached on both coronary mouths in 10 cases, producing atresia or stenosis. Only one ostium was affected in 2 cases, the other being normal. The right coronary artery tended to show the greater degree of involvement. A syphilitic lesion of one mouth and a sclerotic lesion of the other were present in 1 heart. Both coronary mouths were narrowed by sclerosis in 1 heart. The mouths were normal in 3 hearts. There was not a close relation between the valvulitis and the ostial lesion. Two of the 3 hearts with normal coronary mouths had combined syphilitic and rheumatic lesions of the aortic valve.

The main coronary arteries as a whole showed few changes. In 11 hearts they were either perfectly normal or showed only slight focal atheroma. One heart had moderate arteriosclerosis. The coronary arteries in 2 hearts were markedly sclerotic, one with both old and recent thrombosis.

The intrinsic coronary arteries were normal in 9 hearts. Coccal emboli were present in 3 hearts, 2 with acute endocarditis and 1 with neither acute endocarditis nor pericarditis. Acute rheumatic lesions were found in 2 hearts, fulminant in 1

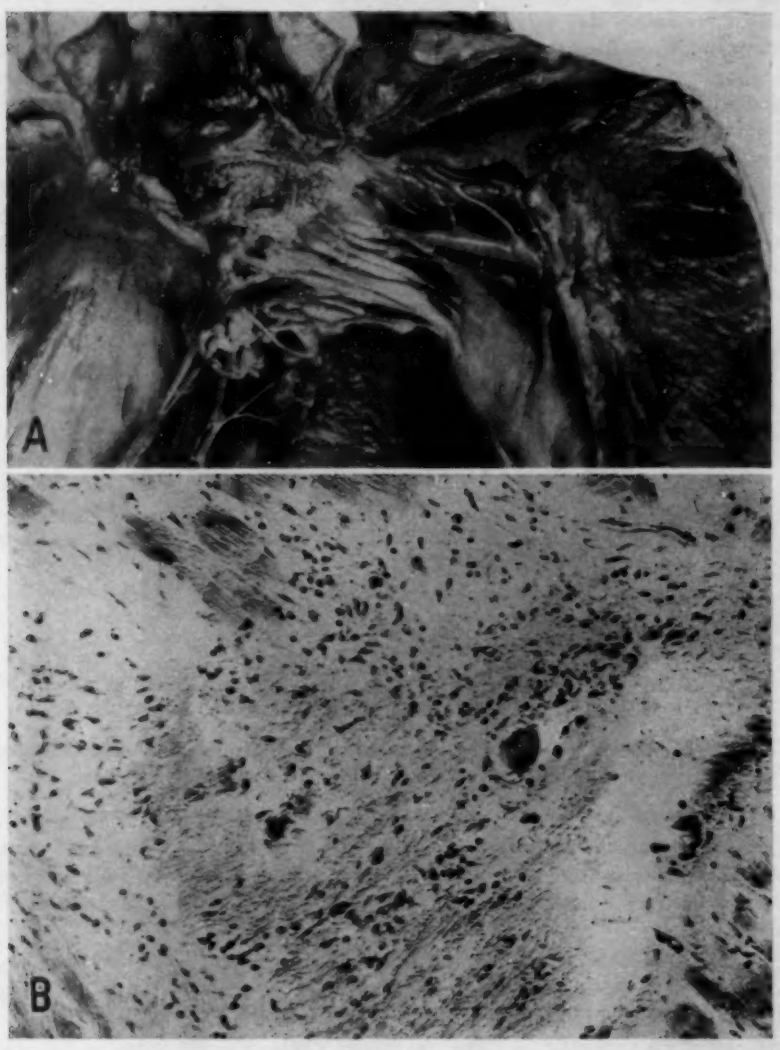

Fig. 2.—*A*, chronic syphilitic granuloma of the body of the anterior mitral leaflet, syphilitic aortic valvulitis and chronic rheumatic disease of the mitral valve. One commissure had an acute exudate in which cocci were demonstrated. *B*, chronic granulomatous myocarditis of undetermined cause; view of a lesion in the left ventricle.

with acute necrosis of the wall and infiltration by polymorphonuclear cells. Acute nonspecific arteritis was present in another. Marked medial hypertrophy was found

in 2 hearts, 1 of which had old and recent thrombi. Of these 2 hearts, the main coronary arteries were only moderately sclerotic in 1; they were markedly sclerotic in the heart with intrinsic thrombi.

Myocardial Aschoff bodies were found in 11 of the 14 hearts; they were extraordinarily numerous and widespread in 6. One heart displayed an unusual localization beneath the endocardium of the left ventricle. In 2 hearts a marked tendency toward healing was evident. Five hearts had only a few Aschoff bodies, sometimes very acute, sometimes healing.

Acute interstitial myocarditis characterized by a polymorphonuclear infiltrate was present in 4 hearts, very extensive in 2 and moderately widespread in 2.

Acute myocardial abscesses were found in 2 hearts. One had a ruptured mycotic aneurysm of the descending branch of the left coronary artery, in which cocci were demonstrable.

Acute massive infarction was present once. Acute miliary infarctions were found in 4 other hearts. Acute miliary necroses were present in 5, in 1 of which they were the predominant lesion.

Chronic granulomatous myocarditis characterized by lymphoid and plasma cells was present in 2 hearts. It was fairly widespread. Spirochetal stains were negative. The cause remained obscure.

One heart had a very unusual granulomatous lesion (fig. 2*B*). The predominant feature was the presence of many giant cells lying in a slightly fibrotic background and intermingled with polymorphonuclears, eosinophils and lymphoid cells. The giant cells did not resemble muscle clubs of regenerating myocardium. The spirochetal, Ziehl-Neelsen and Gram stains failed to reveal organisms. The cause could not be determined.

One heart showed only diffuse degenerative change of the muscle without cellular reaction.

The myocardial lesions never occurred singly, and sometimes it proved difficult to determine which was the more important. An attempt was made, however, to evaluate the lesions of the heart and to determine which were the more prominent in the entire series. Two types seemed to predominate, one aortic valvulitis, the other rheumatic mitral valvulitis. Acute rheumatic myocarditis ranked third and nonspecific myocardial lesions fourth.

The chief complaints which induced the patients to seek medical advice were primarily cardiac in nature. Dyspnea was the most frequent, 11 patients mentioning it. Only 4 patients complained of precordial pain. The other symptoms were simply those common to all cardiac diseases. No symptom or group of symptoms was suggestive of the etiologic factors. Precordial pain was the most suggestive, but its infrequent occurrence rendered it of limited value. The anginal syndrome dominated the picture in only 1 instance. Of seeming significance was the fact that few other cardiovascular symptoms in addition to those specifically noted by the patient could be uncovered by careful questioning.

Acute infections immediately preceded the onset of cardiac failure in 9 instances. In 4 failure followed acute pneumonia; in 4 it followed acute infection of the upper respiratory tract. In 1 case there were recurrent attacks of acute polyarthritis. There probably was antecedent infection in 4 others, since the necropsies revealed acute glomerulitis (1 case) and acute endocarditis (3 cases).

The past personal histories were entirely negative either for rheumatic disease or for syphilis in 6 cases. Three patients said that they had had both rheumatic fever and chancre. Chorea preceded a chancre in a fourth. Rheumatic fever and antisyphilitic therapy were given in the history of a fifth who denied knowledge of

acquiring syphilis. Another patient with a history of rheumatic fever had had six miscarriages. One patient had a history only of rheumatic fever; another, only of chancre. There was no apparent time relation between the onset of either infection and the cardiac decompensation. The interval varied from one to twenty-five years. The same findings were observed in the cases reported in the literature.

The duration of life after the onset of cardiac failure varied from one week to four years. The great majority of the patients died within one and a half years. The shortest duration was one week—in a patient with acute myelogenous leukemia; 8 others lived one year or less, 3 one and a half years, 1 two and 1 four years. It was of interest to note that the greatest number of periods of decompensation was four and the average slightly less than two. Many patients never recovered from the first decompensation. The rapid course of cardiac failure was a striking feature in other reported cases also. Usually the duration of life proved to be a matter only of weeks or months.

The principal cardiac findings were enlargement and murmurs at the apex and the base. The apical murmurs corresponded to the lesions of the mitral valve. A close relation between the aortic valvular lesions and the murmurs could not be demonstrated.

Stigmas of syphilis, usually neurologic, were present in 6 cases. The pupils were either sluggish or irregular in 4, and tendon reflexes were absent in 1. In 1 case vulvar condylomas were present.

The average blood pressure was 140 systolic and 55 diastolic. Six patients had systolic pressures over 150; 5 had a Corrigan pulse. A high pulse pressure appeared of more significance than the actual manometric reading.

Serologic examinations were done on the blood serum of 11 patients. They all proved strongly positive on one or more occasions.

Blood cultures were taken in 4 cases. They revealed streptococci of various types, and all the patients had acute or subacute endocarditis.

Electrocardiographic studies were carried out in 11 cases. Arrhythmias were never found. Predominant right ventricular deviation was present in 1 case; the heart was almost entirely mitralized, and the aortic valvular lesion was minimal. In 4 cases in which there was left ventricular preponderance there was severe aortic valvulitis either of a syphilitic or of a combined rheumatic and syphilitic nature. In 2 cases in which there was left ventricular preponderance and 4 in which there was no deviation it was difficult to correlate the tracings with the lesions. The common factor was extensive myocardial disease due either to inflammation or to coronary ostial atresia. The valvular lesions appeared to play a minor role.

Roentgenologic examinations were carried out in 11 cases. The changes observed in each instance corresponded fairly closely to the gross anatomic appearance of the heart seen at autopsy. The rheumatic conformation was present in 2 cases; in both there were stenotic mitral valves and minor commissural lesions. The conformation of an aortic valvular lesion was found in 1 case, with a grossly incompetent valve; the rheumatic disease was discovered only histologically. Conformations due to aortic incompetency and mitral stenosis or regurgitation in various combinations were found in 5 cases. They corresponded only approximately to the necropsy observations. The studies failed to indicate the true condition in 3 instances; in 2 there was extensive inflammatory disease of the muscle and in the third, severe damage from coronary ostial atresia.

The course of the disease tended to be steadily progressive and the response to therapy poor. In 1 patient leukemia enhanced the process. Three patients died primarily from septicemia. In another patient extensive venous thromboses added

to the burden on the heart. Twelve patients never responded to any type of therapy. Two patients did fairly well until acute endocarditis developed.

The clinical diagnosis of combined syphilis and rheumatic disease as the cause of cardiac dysfunction is difficult to make. In the present series it was made only once. In most of the cases the disease was interpreted as rheumatic, and the syphilis was thought to play a minor role. In case 1 of Swanson a correct diagnosis was made on the basis of a stenotic aortic lesion, an aneurysm of the aorta and a positive Wassermann reaction. The aortic valve was not involved in the syphilitic process. The problem is even more difficult in the type of case under consideration in this communication. From our own data certain findings appear to assume some importance. A history positive for both rheumatic fever and syphilis is very suggestive in any case of cardiac dysfunction. In the physical examination, the apical murmurs of mitral stenosis seemed the most important observation. Almost half the patients had neurologic stigmas of syphilis. Of the laboratory procedures, the serologic and the roentgenologic were the most important. Probably the most important of all is to bear in mind the possibility of the two conditions occurring together. As Swanson has stated, it should be suspected especially in cases in which the course of rheumatic fever is shorter than usual and in those cases in which there is a history of rheumatic disease and clinical evidence of syphilis.

SUMMARY

Fourteen cases of combined syphilitic aortic valvulitis and rheumatic heart disease are reported. In 9 instances the aortic valve was affected by both a syphilitic and a rheumatic process. Ten of the hearts had some degree of involvement of the coronary ostia by syphilis. The myocardium was affected by a multiplicity of lesions. The course tended to be of short duration and was usually intractable to therapy. A clinical diagnosis of the combined disease is difficult to make. It should be suspected in the patient with cardiac disease when a history both of rheumatic fever and of syphilis is obtained, in a patient known to be rheumatic with a course more intractable than usual if there is positive serologic or clinical evidence of syphilis and in a patient with recognized syphilis when the physical findings are those of rheumatic heart disease. The roentgenologic examination can be of great value.

TOXIC EFFECTS OF THE BITTER-TASTING PHENYLTHIOCARBAMIDE

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Self selection nutritional studies have shown thus far that, in general, rats eat substances which nourish them and avoid substances which have injurious effects. This is true provided that the substances are offered in purified form. Thus it was found that rats eat sugars (dextrose, sucrose, maltose, levulose), minerals (sodium chloride, calcium lactate) and vitamins (thiamine chloride, riboflavin, pyridoxine pantothenic acid). They will not, however, take mercuric chloride, morphine sulfate or arsenic trioxide even when these are offered in very small doses, 1 part to 100,000 parts of water.[1] The results obtained so far indicate that the purified substances which the rats eat voluntarily have a palatable taste and are nutritional to human beings, while those which they refuse have an unpleasant taste and injurious effects.

To throw further light on this relation between the taste of a purified substance and its nutritional value, we have undertaken a study of a wide variety of pleasant-tasting and unpleasant-tasting substances. The present report deals with the bitter-tasting phenylthiocarbamide, which has been used extensively for genetic studies on taste in human beings but regarding the pharmacologic action of which almost nothing is known. Does this extremely bitter-tasting substance have any toxic effects?

For these studies we used rats. Observations were made on the acute and chronic effects produced by this substance.

METHODS

The phenylthiocarbamide crystals (C. P., Eimer and Amend) used for these experiments were soluble in water at room temperature to the extent of 0.25 Gm. per hundred cubic centimeters.

In preliminary experiments a few phenylthiocarbamide crystals on the end of a toothpick were placed on the rat's tongue. In later experiments the dose of

From the Psychobiological Laboratory, Phipps Psychiatric Clinic, Johns Hopkins Hospital.

1. Richter, C. P., and Campbell, K. H.: J. Nutrition **20**:31, 1940. Richter, C. P.: Am. J. Psychiat. **97**:878, 1941. Richter, C. P., and Hawkes, C. D.: Am. J. Physiol. **131**:639, 1941.

phenylthiocarbamide was given by stomach tube, subcutaneously, intraperitoneally or in the food or the drinking water.

When an animal died or was killed, it was subjected to a complete autopsy. The various glands and organs were weighed and preserved for histologic study. A total of 51 rats was used.

RESULTS

Acute Effects.—In the preliminary experiments we found that minute amounts of phenylthiocarbamide crystals placed on the tongues of rats regularly caused them to die within a few hours. The administration of measured amounts of the crystals either by injection or by forced feeding later confirmed these earlier results.

TABLE 1.—*Survival Times of Rats Used in Acute Experiments*

Rat	Weight, Mg.	Amount of Phenylthiocarbamide Administered, Mg.	Survival Time, Hr.	Method of Administration
1	182	1	8	Intraperitoneal injection
2	169	2	15	Intraperitoneal injection
3	164	3	8	Intraperitoneal injection
4	170	3	5	Stomach tube
5	185	4	18	Stomach tube
6	178	5	7	Stomach tube
7	174	5	9	Intraperitoneal injection
8	185	6	8	Stomach tube
9	185	7	5	Stomach tube
10	350	7.5	2	Stomach tube
11	350	7.5	2	Stomach tube
12	350	7.5	2	Stomach tube
13	350	7.5	4	Stomach tube
14	350	7.5	6	Stomach tube
15	180	7.5	6	Intraperitoneal injection
16	180	7.5	7	Subcutaneous injection
17	182	10	13	Stomach tube
18	174	10	10	Intraperitoneal injection

Table 1 summarizes the observations made on 18 rats, all of which died. The amounts of phenylthiocarbamide crystals received by the rats ranged from 1.0 to 10.0 mg.; their survival times, from two to eighteen hours. No correlation was found between dose, weight and survival time nor between method of administration (whether by injection or by stomach tube) and survival time. One of the rats which received 3.0 mg. lived only five hours, while another which received 10.0 mg. lived thirteen hours. In order to determine the median lethal dose, further experiments were made on 8 rats. Each rat was given 0.5 mg. in a 0.01 per cent water solution by stomach tube. Not a rat died. Thus, the median lethal dose must fall near 1.0 mg.

All the rats showed marked respiratory distress and were inactive and cold. Their body temperatures often dropped from an average level of 101.0 F. to levels as low as 94.0 F. in less than thirty minutes. Approximately 50 per cent of the rats died in convulsions.

The only detectable pathologic changes found at autopsy in the 18 rats that died were marked edema of the lungs and pleural effusion. The amounts of fluid in the thoracic cavities ranged from 6 to 14 cc., which is practically the same as the total blood volume for animals of this size. As much as 10 cc. was collected from some of the rats which lived only two to three hours. The fluid was clear and serous, and coagulated after it came into contact with the air. The centrifuged sediment showed only occasional lymphocytic and mononuclear cells. Denis and Minot [2] and Loeb, Atchley and Palmer [3] stated that nonprotein transudates are approximately the same chemically as the blood serum. In the few studies in which we compared the blood and the pleural effusion of rats killed at definite intervals, we usually found somewhat higher values for the blood than for the effusion. However, the difference was not great enough to be in disagreement with the aforementioned statement.

The chemical analysis of the pleural effusion showed an increase in nonprotein nitrogen in direct proportion to the increase in survival time. Thus, the fluid of an animal with a two hour survival time had a nonprotein nitrogen content of 39 mg. per hundred cubic centimeters, while that of an animal living thirteen hours had a content of 100 mg. per hundred cubic centimeters. The urea nitrogen was not increased over 6.5 mg. Uric acid, sugar and the electrolytes of the pleural fluid were essentially normal as judged by the chemical composition of normal rat blood.

Chronic Effects.—In these experiments 26 adult rats (16 females and 10 males) were used. The ages ranged from 109 to 167 days; the weights, from 180 to 233 Gm. (females) and from 340 to 378 Gm. (males). Of the 26 rats, 23 received the phenylthiocarbamide in their drinking water, while the remaining 3 animals were given the drug mixed with their regular food. At the outset the amount of the crystals mixed in the food or water ranged from 0.1 mg. to 0.25 mg. per gram of food or per cubic centimeter of water. Three of the rats died within twelve hours from pulmonary edema and pleural effusion such as were observed in the acute experiments. Four of the rats exhibited labored breathing and sharp falls in body temperature during the first twenty-four hours, but they recovered and continued to be used in the experiment. It is to be noted that the 3 animals which died were all receiving only 0.1 mg. of the drug per cubic centimeter of water and it may well be that this concentration was below their taste threshold (4.5 per cent of the animals tested had thresholds above this concentration).[4] Thereafter at intervals of five to fifteen days the concentration of the solution

2. Denis, W., and Minot, A. S.: Arch. Int. Med. **20**:879, 1917.

3. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: J. Gen. Physiol. **4**:591, 1922.

4. Richter, C. P., and Campbell, K. H.: Am. J. Physiol. **134**:157, 1941.

was increased in small steps, depending on the effects produced on the body weight and on the food and water intake. The best results were obtained when the concentrations were increased in the following steps: 0.01, 0.02, 0.04, 0.06 and 0.10 Gm. per hundred cubic centimeters or grams at ten day intervals. By drinking less water or by eating less food, even when the water or food contained only small amounts of phenylthiocarbamide crystals, the rats indicated that they did not like the bitter-tasting chemical.

Figure 1 gives the records of water intake, body weight and body temperature of a typical rat. It also gives the average daily intake of phenylthiocarbamide crystals for the periods during which each dosage was given. This rat received the drug in its drinking water. For ten

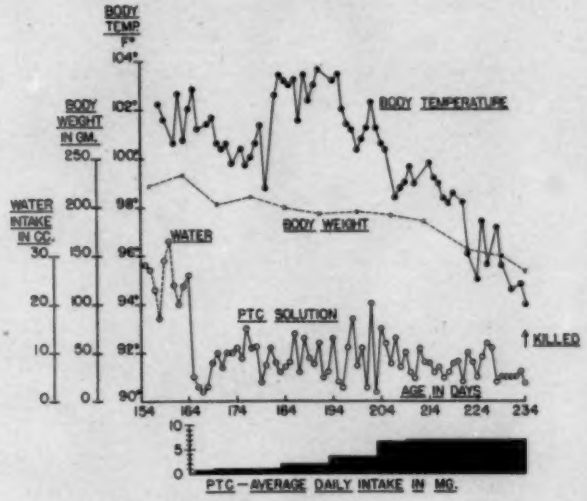

Fig. 1.—Water intake, weight and temperature of a rat receiving phenylthiocarbamide (PTC) in its drinking water.

days before the administration of the drug was started, the daily water intake averaged 24.8 cc. For the first four days of the administration of the drug the intake dropped below 5.0 cc. In the following few days it increased to 6.0 cc.—a level at which it remained fairly constant for fifty days. The rat lost weight quite rapidly during the first ten days, then less rapidly for the next forty days, and more rapidly again during the last twenty days. The body temperature averaged 101.7 F. in the ten days prior to the administration of the drug. During the first fifteen days after the administration was started the body temperature decreased to a level near 100.0 F., then increased for fourteen days to a level near 103.0 F., which was above the original level. During the next forty days it decreased steadily, finally reaching 94.0 F. on the day the rat was killed.

Table 2 summarizes the results of the observations made on 16 rats, 13 of which received phenylthiocarbamide in their drinking water, and 3, in their food. The duration of the treatment ranged from twenty-one to eighty days. The amounts of the crystals which the rats received during the first ten days averaged 1.1 mg. per rat per day and ranged from 0.6 to 1.7 mg.; during the last ten days the amounts averaged 6.8 mg. and ranged from 0.3 to 12.6 mg. These results show that the rats acquired a greatly increased tolerance for the drug.

The daily water intakes averaged 26.0 cc. for the ten days before treatment, 9.0 cc. for the first ten days of administration of the drug

TABLE 2.—*Summary of Observations on 16 Rats*

Rat	Age at Start, Days	Treatment, Days	Average Daily Intake of Phenylthiocarbamide, Mg.		Average Daily Fluid Intake, Cc.			Average Daily Food Intake, Gm.		Body Weight, Gm.		Body Temperature, F.		
			First 10 Days	Last 10 Days	10 Days Before	First 10 Days	Last 10 Days	First 10 Days	Last 10 Days	Start	End	10 Days Before	Last 10 Days	Lowest
1 ♀	116	21	0.7	0.3	21.5	7.4	0.3	...	...	180	100	102.0	95.0	94.0
2 ♀	119	29	0.7	1.2	28.9	7.0	1.2	...	...	200	100	100.5	95.0	94.8
3 ♂	165	44	1.2	2.3	26.0	9.5	3.9	...	...	378	248	99.7	96.8	95.8
4 ♂	165	44	1.7	6.4	30.5	15.1	13.5	...	...	340	241	99.0	98.0	96.6
5 ♀	165	57	0.8	9.4	23.7	6.1	9.1	...	...	222	126	101.2	98.0	95.1
6 ♂	165	58	1.7	6.9	30.7	13.2	7.0	...	...	345	181	98.5	98.9	95.9
7 ♂	165	61	1.6	7.5	28.7	12.8	6.9	...	...	356	155	100.4	96.2	94.2
8 ♀	167	63	0.9	5.3	....	8.9	4.6	...	...	190	105	.....	....	....
9 ♀	166	63	1.1	10.8	....	11.0	9.5	...	...	195	162	.....	....	....
10 ♀	166	63	1.0	6.0	....	10.1	4.5	...	...	185	107	.....	....	....
11 ♀	166	63	1.3	7.5	....	**14.3***	**15.3**	4.6	3.7	180	128	.....	....	....
12 ♀	166	63	0.9	8.6	....	**21.5**	**13.6**	4.4	3.4	140	96	.....	....	....
13 ♀	167	63	1.6	10.8	....	**17.9**	**16.9**	6.8	5.1	180	128	.....	....	....
14 ♀	165	70	0.8	7.0	24.8	6.9	6.6	...	...	233	135	100.7	95.6	94.0
15 ♀	100	80	0.6	6.3	18.0	6.4	6.3	...	...	180	146	98.9	97.2	95.0
16 ♀	109	80	0.9	12.6	20.0	8.7	12.6	...	...	190	128	101.6	97.4	95.6
Average			1.1	6.8	26.0	9.0	7.0	5.2	4.1	...	....	100.3	96.7	95.1

* The bold face figures are not included in the average. These rats received the crystals in their food.

and 7.0 cc. for the last ten days. These averages do not include the records of the 3 rats which received the crystals in their food. The water intakes of these 3 rats averaged 17.9 cc. for the first ten days and 15.9 cc. for the last ten days, and the daily food intakes averaged 5.2 Gm. for the first ten days and 4.1 Gm. for the last ten days, and it is presumably the decrease in food intake which accounts for the reduction in the water consumption of these animals. The food intake was not measured before treatment was started, but that of the normal adult rat in this laboratory ranges from 13 to 14 Gm. per day. The presence of the phenylthiocarbamide crystals in the food thus greatly reduced the intake. The body weights of all the animals decreased markedly. The losses ranged from 33 to 200 Gm., or from 17 to 56 per cent. The body temperatures

averaged 100.3 F. for the ten days before treatment and 96.7 F. for the last ten days. The lowest temperatures reached ranged from 96.6 to 94.0 F. and averaged 95.1 F.

The rats which had received phenylthiocarbamide for long periods of time and which had shown sharply decreasing body temperatures and weights revealed almost complete atrophy of the thymus glands, atrophy

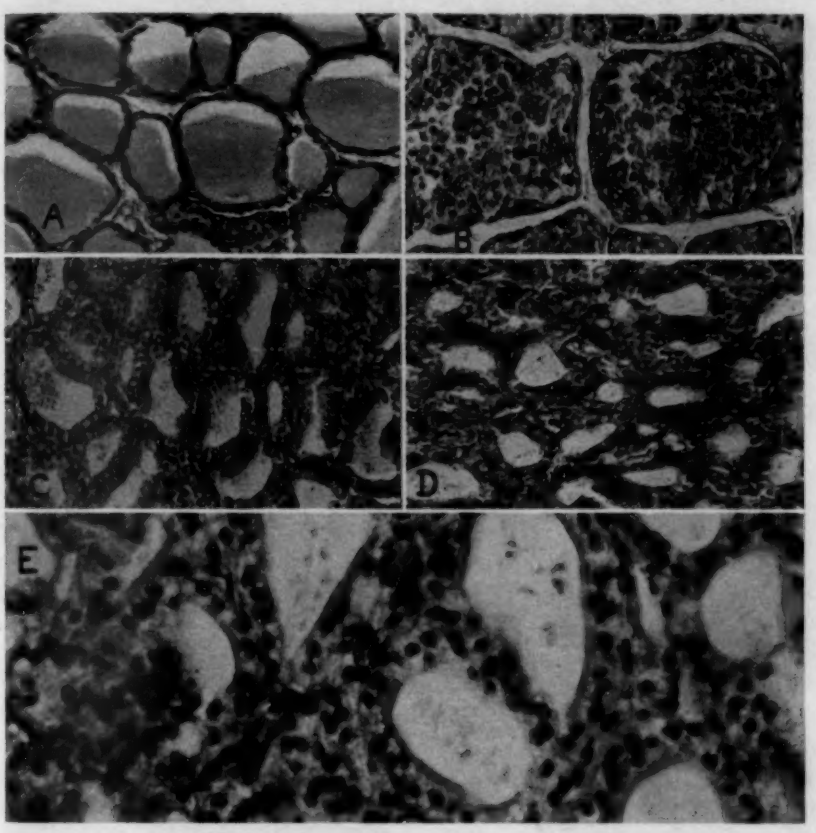

Fig. 2.—*A*, thyroid of a normal rat; × 150. *B*, thyroid of rat chronically poisoned with phenylthiocarbamide; × 150. *C*, *D*, *E*, hyperplasia of the thyroid glands of rats chronically poisoned with phenylthiocarbamide. *C* and *D*, × 150; *E*, × 400.

of the ovaries and marked hypertrophy of the thyroid glands. Almost every thyroid gland examined was hyperemic and so much hypertrophied that the isthmus stood out like a thick band across the trachea. The degree of hypertrophy varied roughly with the amount of the drug received. It was found that handling of the thyroid glands interfered with the interpretations of histologic sections because of the increased

fragility of the glands. Accordingly, in most cases the thyroid gland was removed intact with the trachea and fixed in 10 per cent solution of formaldehyde U. S. P. before being separated from the trachea for sectioning. Six thyroid glands were weighed. The weights ranged from 31 to 65 mg. The actual weights of 4 of these glands were much above the normal; when the weights were calculated per kilogram of body weight, all 6 thyroid glands exceeded the range of variation found in normal thyroid glands, varying from 188 to 508 mg. as against 106 to 164 mg.

Histologic study of the endocrine glands of these rats revealed alterations only in the thyroid glands. The follicles were small, irregular in shape and nearly completely devoid of colloid. The epithelial layer

Fig. 3.—Black rat beginning to turn gray after fifty days of chronic phenylthiocarbamide poisoning.

showed high columnar cells with large round nuclei. In spite of the fact that the glands were removed with as little handling as possible, many of the cells had become freed from their attachments and either completely or nearly completely filled the follicles, making it difficult to define the lumens. In figure 2 *A* and *B* are photographs at magnifications of 150 of typical sections of the thyroid glands of a normal rat and a rat chronically poisoned with phenylthiocarbamide.

Did the thyroid gland show this same picture during the earlier stages of treatment, while the body temperature was still high? In a group of 7 rats which had been treated for fifty-five days, at which time the temperatures averaged 100.0 F., one lobe of each thyroid gland was removed. These lobes were found to be uniformly hyperemic and hypertrophied. Some of the single lobes weighed as much as 53 mg.

Histologically, they showed typical hyperplasia. The cells had not become detached in any of these glands. *C* and *D* in figure 2 are sections from 2 glands at magnifications of 150 and *E* is a section of another gland at a magnification of 400. The high columnar epithelium can be clearly seen. Almost all stages of budding of the epithelium and extension of the cell layers across the follicles for the formation of new follicles were present. Colloid was absent in most of the follicles. This picture of hyperplasia was found in all 7 glands that were removed.

Externally, the chronically poisoned rats showed coarsening of the hair with an increase in prominence of the guard hairs, spectacle eyes and thinning of the hair on the nose followed by the formation of crusted sores. Two black rats began to turn gray approximately forty to fifty days after the start of treatment. Figure 3 shows the photograph of one of these animals taken near the eightieth day of treatment. As the other rats were either buff or white, graying was not detected. Two rats showed tremors of the type seen in parathyroid-deficient rats. Morgan and Simms [5] reported damage to the adrenal and thyroid glands in rats fed a basal diet deficient in the filtrate factor of the B complex. They found that the abnormality of the thyroid gland was in direct relation to the extent of graying fur. Treatment with thyroid extract caused the graying to disappear after fifteen weeks.

COMMENT

These experimental observations show that phenylthiocarbamide has an extremely toxic effect on rats, doses of 1.0 to 2.0 mg. causing death in only a few hours. Whether it has an equally toxic effect on human beings and other animals is not known.

These observations provide another instance of the close relation between the taste of purified substances and their nutritional value. That this bitter-tasting substance has such a toxic effect does not mean that all other bitter-tasting substances also have toxic effects. Undoubtedly, further research will reveal a variety of bitter tastes associated with quite different and not necessarily injurious effects. The bitter taste of such substances as riboflavin and quinine may differ markedly from the phenylthiocarbamide taste.

The possible danger involved in the use of phenylthiocarbamide may have to be taken into account in the genetic studies in which this substance is used on human beings. However, the amount used for a single threshold test is so small that the appearance of toxic effects would seem unlikely. In giving repeated tests over several weeks or months, the toxic action should undoubtedly be considered. Caution may also have to be exercised in factories in which phenylthiocarbamide is used for

5. Morgan, A. F., and Simms, H. D.: J. Nutrition **19**:233, 1940.

industrial purposes. Further, since approximately 5 per cent of the persons tested do not taste the chemical except very transiently [6] and since these nontasters also may not be able to taste other bitter-tasting toxic substances, some precautions may have to be taken to warn them against these substances, just as color blind persons are helped by special traffic markings.

We were unable to determine the cause of death of the rats used in the acute experiments. Pulmonary effusion may have been produced either directly by an attack of the phenylthiocarbamide on the pulmonary tissues, capillaries or lymphatic vessels or indirectly through left-sided heart failure. The part played by the sharp drop in body temperature must also be investigated. It seems likely that the pulmonary effusion and accompanying respiratory distress produced profound shock, lowering the metabolism and indirectly the body temperature. It is possible, however, that both the pulmonary effusion and the lowering of body temperature resulted from a common cause, a direct attack of the drug on the metabolic centers in the central nervous system. However, in the brain sections of a few rats we have not been able to detect any pathologic changes.

We have found no other reports of pulmonary edema with pleural effusion produced chemically. Glaubach and Pick [7] and Cramer [8] found that tetrahydro-β-naphthylamine injected into guinea pigs and rats which previously had been treated with thyroxin produced localized edema and hemorrhage in the lungs. Hanzlik [9] and Hanzlik and Tainter [10] found that paraphenylenediamine injected into rabbits produced an edematous condition confined to the head and neck. Although the latter substance is toxic to rats, it does not produce edema in them.

The results of these experiments also demonstrated that when the dose was increased gradually the tolerance to the drug was greatly increased. After sixty days on progressively larger doses, the rats did not die even when they took as much as 16 mg. per day.

The prolonged administration of phenylthiocarbamide increased the weights of the thyroid glands, which showed consistent pictures of hyperplasia that may have been the result of either a direct action of the drug on the glands or a compensatory reaction of the glands to the lowered body temperatures. The evidence at hand favors the latter explanation.

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6. Blakeslee, A. F.: Proc. Nat. Acad. Sc. **18**:120, 1932. Salmon, T. N., and Blakeslee, A. F.: Proc. Nat. Acad. Sc. **21**:78, 1935. Richter and Campbell.[4]

7. Glaubach, S., and Pick, E. P.: Arch. f. exper. Path. u. Pharmakol. **151**: 341, 1930.

8. Cramer, W.: Brit. J. Exper. Path. **1**:31, 1920.

9. Hanzlik, P. J.: J. Indust. Hyg. **4**:386, 1923.

10. Hanzlik, P. J., and Tainter, M. L.: J. Pharmacol. & Exper. Therap. **24**: 179, 1924.

It is known that a cold external temperature stimulates the thyroid gland. Presumably a lowered internal temperature likewise increases thyroid activity.

It seems likely that the typical picture of hyperplasia with the high and regular epithelial layers found in the thyroid glands, removed when the rats still showed elevated temperatures and before they had started to lose weight rapidly, resulted from the effort of the glands to counteract the effects of the phenylthiocarbamide and that the histologic picture found in the terminal stages after the temperatures and weights had decreased to low levels indicated a state of exhaustion.

Chesney and his collaborators [11] observed a remarkably great enlargement of the thyroid glands of rabbits which had been kept on a high cabbage diet. The glands of some of these rabbits weighed over 40 Gm., whereas those of normal animals averaged only 0.23 Gm. and did not exceed 1.73 Gm. The glands showed a greatly reduced colloid content, small follicles, columnar epithelial cells and poorly defined lumens which were almost entirely filled with epithelial cells. The basal metabolic rates of such animals fell below normal; iodine increased the rates and caused involution of the hyperplastic thyroid glands, but in most instances the animals died. Webster and Chesney [12] found that iodine when administered sufficiently early prevented all the toxic manifestations. Marine, Baumann, Spence and Cipra,[13] who confirmed the findings of Chesney and co-workers,[14] later found that other members of the Brassica group, as well as cabbage, produced enlargement of the thyroid gland in rabbits and that the production of the goitrous condition depended on the large amounts of cyanides present in these plants.

Histologically, the thyroid glands of these animals closely resembled the glands of the rats which had been kept on phenylthiocarbamide until their body weights and temperatures had decreased far below the normal levels. In both instances the lumens of the follicles were poorly defined and almost entirely filled with apparently detached large round epithelial cells and contained no colloid. Chesney and co-workers [14] did not record the body temperatures. It would be interesting to know whether their rabbits also had depressed temperatures. None of the rabbit thyroid glands showed the budding of the epithelium and the other characteristics of the phenylthiocarbamide-treated rats which still showed elevated body temperatures.

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11. Chesney, A. M.; Clawson, T. A., and Webster, B.: Bull. Johns Hopkins Hosp. **43**:261, 1928.

12. Webster, B., and Chesney, A. M.: Bull. Johns Hopkins Hosp. **43**:291, 1928; Am. J. Path. **6**:275, 1930.

13. Marine, D.; Baumann, E. J.; Spence, A. W., and Cipra, A.: Proc. Soc. Exper. Biol. & Med. **29**:772, 1932.

14. Chesney and others.[11] Webster and Chesney.[12]

None of the rats given phenylthiocarbamide showed exophthalmos. Marine, Rosen and Cipra [15] and Marine, Spence and Cipra [16] reported that bilateral exophthalmos can be produced in prepubertal rabbits with methyl cyanide and that the effect can be prevented by administering either iodine or concentrates of the juices of fresh plants and fruits (ascorbic acid). The same treatment did not produce exopthalmos in mature rabbits. Spence and Marine [17] found that mice and rats were more resistant to methyl cyanide and stated that the animals were resistant to goitrogenic substances in general.

Other workers, including McCarrison,[18] Sharpless,[19] Wilgus and co-workers [20] and Levine and co-workers,[21] have reported various agents capable of producing conditions of thyroid hyperplasia which may or may not be similar to those found in the present experiments. Owing to the confusion in terminology, amounting in some cases to actual contradiction, it has not been possible to compare these various effects with those produced by feeding phenylthiocarbamide.

SUMMARY

Minute amounts of the bitter-tasting phenylthiocarbamide killed rats whether administered orally, by injection or by stomach tube. Eighteen rats given 1.0 to 10.0 mg. doses of the chemical died; 8 rats given 0.5 mg. survived. Thus, the median lethal dose for adult rats fell near 1.0 mg. The poisoned rats died in two to eighteen hours with marked respiratory distress and sharp decreases in body temperature to levels as low as 94.0 F. At autopsy the thoracic cavity was found to be filled with a clear serous fluid (6 to 14 cc.) and the lungs were edematous. This edema was limited strictly to the lungs. Pathologic changes were not found in any other parts of the body. Administration of the drug in progressively larger amounts over twenty to eighty day periods increased the tolerance to an average of 10.0 to 12.0 mg. per day.

The body temperatures of these chronically poisoned rats first became subnormal (fifteen days), then elevated (ten to thirty days) and finally dropped to very low levels (96.6 F. to 94.0 F.). The body

15. Marine, D.; Rosen, S. H., and Cipra, A.: Proc. Soc. Exper. Biol. & Med. **30**:649, 1933.

16. Marine, D.; Spence, A. W., and Cipra, A.: Proc. Soc. Exper. Biol. & Med. **29**:822, 1932.

17. Spence, A. W., and Marine, D.: Proc. Soc. Exper. Biol. & Med. **29**:967, 1932.

18. McCarrison, R.: Brit. M. J. **2**:671, 1933; **1**:29, 1937.

19. Sharpless, G. R.: Proc. Soc. Exper. Biol. & Med. **38**:166, 1938.

20. Wilgus, H. S., Jr.; Gassner, F. X.; Patton, A. R., and Gustavson, R. G.: J. Nutrition **22**:43, 1941.

21. Levine, H.; Remington, R. E., and von Kolnitz, H.: J. Nutrition **6**:347, 1933.

weights remained essentially unchanged for twenty to forty days, then dropped sharply. Some of these rats showed tremors of the parathyroid deficiency type. Two black rats showed striking graying of the hair in large areas over the back and head.

At autopsy the rats showed markedly hypertrophied and hyperemic thyroid glands. The thymuses and ovaries showed marked atrophy; the other glands showed no definite changes. Thyroid glands removed from rats while the body temperatures were still elevated and before the weights showed a sharp decrease presented a typical picture of hyperplasia. The follicles were very small, irregular in shape and devoid of colloid; the epithelial cells were high and columnar and showed all stages of budding, even to the formation of new follicles; the nuclei were large and round, and mitoses were frequent. Thyroid glands removed from rats which had reached the terminal stages, with low body temperatures and great losses in weight, showed a somewhat different histologic picture. The chief difference was that almost all of the epithelial cells had become dislodged from their normal position and almost completely filled the lumens of the follicles.

It seemed likely that the definitely hyperactive picture of the thyroid gland resulted from an effort of the organism to compensate for the reduction of metabolism produced by the drug and that the picture shown during the terminal stages represented a state of exhaustion.

EXPERIMENTAL ATHEROSCLEROSIS

IV. EFFECT OF TESTOSTERONE PROPIONATE AND ESTRADIOL DIPROPIONATE ON EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

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In view of the chemical similarity of cholesterol to the steroid sex hormones and of the conflicting reports on the influence of these hormones on lipid metabolism in animals,[1] it appeared desirable to determine the effects of some of the steroid sex hormones on cholesterol metabolism in rabbits. In a recent study in this laboratory [2] no noteworthy changes were found in the cholesterol content of the blood or the aorta of the male or the female rabbit receiving 450 mg. of testosterone propionate and 9 mg. of estradiol dipropionate, respectively, in divided doses over a period of one hundred days. To what extent these steroid hormones can influence the production of atherosclerosis in rabbits fed cholesterol is the subject of the present communication.

MATERIAL AND METHODS

The animals used were 28 female and 29 male rabbits, 3 to 5 months old and weighing from 1.0 to 2.0 Kg. The animals were kept in individual cages and were fed each a measured amount of Ralston-Purina chow [2a] once daily. Each rabbit

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This investigation was aided by a grant from the Ciba Pharmaceutical Products Inc., Summit, N. J.

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2. Ludden, J. B.; Bruger, M., and Wright, I. S.: Endocrinology **28**:999, 1941.

2a. The chow contains a mixture of grains and alfalfa hay, supplemented by vitamins and minerals.

received 1 Gm. of cholesterol mixed with the chow three times weekly throughout the experiment. Testosterone propionate and estradiol dipropionate[3] were administered in dilutions so adjusted that each dose was dissolved in 1 cc. of sesame oil. The animals were divided into male and female subgroups receiving (*a*) no injections, (*b*) sesame oil (1 cc.), (*c*) testosterone propionate (10 mg.) and (*d*) estradiol dipropionate (0.2 mg.). The injections were given daily during

TABLE 1.—*Effect of an Androgenic and an Estrogenic Steroid on the Cholesterol Content of the Blood and the Aorta in Male Rabbits Fed Cholesterol*

Rabbit	Blood Cholesterol (Mg. per 100 Cc.) After Given Number of Days										Aorta Cholesterol (Mg. per 100 Gm. Dry Weight)
	0	8	21	35	49	65	76	90	100	Mean*	
Controls—No Injections											
167	84	153	...	202	676	715	658	387	556	436	2509
168	89	119	143	278	603	943	833	915	949	540	2440
169	92	75	329	431	487	815	694	397	...	415	1514
177	68	206	455	431	667	893	962	635	852	575	2620
Controls—Sesame Oil 1 Cc. Three Times Weekly											
103	154	96	205	357	694	568	503	586	...	394	1473
104	150	121	193	318	641	521	615	707	...	408	983
150	178	273	581	514	725	820	1000	904	721	635	1371
151	90	107	308	...	...	472	802	743	540	446	605
152	117	285	676	598	926	1191	1027	862	1000	743	2013
Average										510 ±121	1800 ±777
Testosterone Propionate 10 Mg. Three Times Weekly											
84	87	146	146	313	647	500	407	457	475	353	467
92	108	163	125	114	182	234	164	208	260	180	433
93	97	140	122	237	158	158	176	318	544	216	698
83	109	154	102	109	391	391	357	380	481	275	1423
153	81	125	335	350	667	610	641	500	625	443	2534
154	85	204	272	295	323	426	449	408	475	326	1795
155	91	132	121	245	407	704	843	676	736	439	2336
156	70	272	507	436	...	820	962	833	824	591	2190
158	64	120	390	142	357	514	564	688	882	414	1150
159	63	130	182	131	259	417	517	463	1087	361	1051
175	85	197	122	318	617	658	798	517	926	471	1680
Average										370	1432
Estradiol Dipropionate 0.2 Mg. Three Times Weekly											
22	80	150	260	305	421	383	320	350	544	313	487
23	122	216	399	544	647	750	750	893	1136	606	2371
88	100	163	272	302	335	289	329	308	670	308	1563
140	85	237	379	...	603	725	789	833	591	530	1378
141	83	123	231	141	130	172	235	...	156	159	357
142	97	208	373	500	596	667	600	670	773	498	1178
144	143	323	510	...	781	715	688	586	532	475	1115
145	121	280	595	500	660	1021	1000	773	736	632	729
146	113	226	424	625	667	877	938	949	1027	650	1498
Average										463	1186

* This represents the average of the blood cholesterol values obtained throughout the hundred day period.

the first week and three times weekly during the subsequent thirteen weeks of the experiment.

The whole blood cholesterol was determined every eight to sixteen days by a modified Bloor method.[4] The procedure used for killing the rabbits, the technic

3. The testosterone propionate and estradiol dipropionate were supplied by the Ciba Pharmaceutical Products Inc., Summit, N. J.

4. Sackett, G. E.: J. Biol. Chem. **64**:203, 1925. Mirsky, I. A., and Bruger, M.: J. Lab. & Clin. Med. **18**:304, 1932.

for the removal of the aortas and the determination of the cholesterol contents of the aortas have been described elsewhere.[5]

This report embraces two series of experiments done six months apart. The first series included 9 male and 9 female rabbits, and the second, 20 male and 19 female rabbits. Since the procedures in both series were identical, the results have been grouped together for the sake of clarity.

TABLE 2.—*Effect of an Androgenic and an Estrogenic Steroid on the Cholesterol Content of the Blood and the Aorta in Female Rabbits Fed Cholesterol*

Rabbit	Blood Cholesterol (Mg. per 100 Cc.) After Given Number of Days										Aorta Cholesterol (Mg. per 100 Gm. Dry Weight)
	0	8	21	35	49	65	76	90	100	Mean*	
Controls—No Injections											
178	74	240	197	112	457	510	1000	908	1211	527	1415
G	79	77	332	556	765	789	833	...	892	540	4267
W	63	141	455	735	798	915	1119	...	986	652	3360
Controls—Sesame Oil 1 Cc. Three Times Weekly											
89	92	229	383	508	765	670	636	746	862	550	5982
90	79	228	347	694	750	636	694	631	646	523	2535
108	145	87	282	276	578	313	383	460	...	316	1612
147	91	222	153	463	660	909	1067	902	974	613	2763
149	83	70	223	320	505	938	949	577	682	483	3248
22	149	421	487	481	806	938	893	781	962	658	5020
Average										540 ±108	3356 ±1514
Testosterone Propionate 10 Mg. Three Times Weekly											
28	88	123	268	300	222	391	323	318	252	254	464
29	106	142	128	123	104	129	164	280	280	162	467
160	82	86	218	300	633	820	833	332	349	406	831
161	90	119	206	188	...	650	447	273	263	280	579
162	87	268	490	...	244	510	536	900	487	359	649
164	68	221	74	75	361	477	337	233	410	251	542
165	54	129	70	87	200	213	289	225	308	175	780
166	58	117	75	64	96	153	212	151	199	125	420
176	70	131	110	191	101	191	329	419	701	249	507
Average										251	582
Estradiol Dipropionate 0.2 Mg. Three Times Weekly											
27	92	110	229	175	264	318	289	332	371	242	484
94	74	226	237	295	313	347	295	399	475	296	1029
96	77	155	276	326	230	195	353	391	274	253	638
123	78	313	441	444					died		
133	98	93	106	174	202	326	153	242	229	187	347
134	108	96	100	85	171	347	560	510	635	290	671
104	106	253	295	285	357	506	708	647	750	444	809
108	85	426	357	525	206	347	412	323	127	319	330
111	87	193	350	109	210	310	463	408	551	298	507
117	80	315	500	282	332	446	536	280	272	338	623
Average										294	604

* This represents the average of the blood cholesterol values obtained throughout the hundred day period.

RESULTS

The results are given in tables 1 and 2. The control rabbits receiving no injections and those which received injections of sesame oil have been grouped together since the results failed to indicate that sesame oil specifically influenced the cholesterol content of either the blood or the aorta.

5. Bruger, M., and Fitz, F.: Arch. Path. **25**:637, 1938.

The control male rabbits (table 1) showed a pronounced rise in the blood cholesterol and a marked increase in the cholesterol content of the aorta, although wide variations occurred, as indicated by the rather high standard deviations of the mean values.

The average values for the cholesterol in the blood and the aorta in the male animals given the estrogenic and androgenic steroids were somewhat lower than those noted in the controls. The results, however, cannot be considered as statistically significant.

In the female groups (table 2), however, the development of hypercholesteremia was inhibited in both the testosterone-treated and the estradiol-treated rabbits as compared with the controls. This was associated with an almost complete lack of deposition of cholesterol in the aortas. The cholesterol contents of the aortas were not unlike those observed in the aortas of the noncholesterol-fed animals.[2]

It is of interest to note that in the control groups, although the mean values for the blood cholesterol in the female rabbits were similar to those determined for the male animals, the cholesterol contents of the aortas were much higher in the female group. This observation further accentuates the efficacy of the estrogenic and androgenic steroids in preventing the deposition of cholesterol in the aortas of female rabbits fed cholesterol.

COMMENT

Although several substances have been found to influence the development of experimental atherosclerosis in rabbits, the action of iodine in preventing the deposition of cholesterol in the arterial walls has been most consistently observed.[6] A review of the protocols of Turner [6c] indicates that iodine is equally effective in male and female rabbits. This would imply that the mechanism of action of these steroids is different from that of iodine, since the steroids are effective only in the female rabbit. The observation that the androgen (testosterone) and the estrogen (estradiol) are equally effective in preventing cholesterol deposits in the female animal suggests that both steroids produce a common metabolic effect through some chemical action which takes place in the female but not in the male animal.

Obviously, further experiments are necessary in order to explain this phenomenon and to throw further light on the mechanism of this action. Although the estrogenic and the androgenic steroid used in the present study were injected in amounts larger than those employed clinically (on the basis of relative body weight), these observations,

6. (*a*) Murata, M., and Kataoka, S.: Verhandl. d. japan. path. Gesellsch. **7**:27, 1917. (*b*) Liebig, H.: Arch. f. exper. Path. u. Pharmakol. **159**:265, 1930; **175**:409, 1934. (*c*) Turner, K. B.: J. Exper. Med. **58**:115, 1933. (*d*) Turner, K. B., and Khayat, G. B.: ibid. **58**:127, 1933. (*e*) Page, I. H., and Bernhard, W. G.: Arch. Path. **19**:530, 1935.

nevertheless, may be of clinical significance. For example, the relative infrequency of arteriosclerosis (or marked calcification of the peripheral arteries[7]) in women may depend in part on the efficacy of the ovarian hormone in preventing the deposition of cholesterol in the arterial walls, whereas in men little or no such protective action occurs.

SUMMARY

In female rabbits fed cholesterol the development of hypercholesteremia was inhibited and the deposition of cholesterol in the aorta was prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol these steroids exerted little or no such protective action.

7. Wright, I. S.; Pratt, G., and Lake, M.: Read at the meeting of the American Heart Association, June 1, 1941, to be published.

Forensic Medicine

PULMONARY EMBOLISM CAUSED BY A LEAD BULLET FOLLOWING A GUNSHOT WOUND OF THE ABDOMEN

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The purpose of this paper is to review the literature on projectile embolism and to describe a case of pulmonary embolism caused by a lead bullet following a gunshot wound of the abdomen.

REVIEW OF THE LITERATURE

Examination of the literature revealed 32 cases of projectile embolism. Undoubtedly more have occurred. With respect to some of the cases cited in the following paragraphs, the original reports could not be secured for reference, but the source of information for each is indicated.

The first case of projectile embolism reported was that recorded by Davis [1] in 1834. It was the case of a young man who had a homemade gun with a wooden breech approximately 3 inches (7.5 cm.) long and ⅓ inch (0.85 cm.) in diameter. When he fired this gun, the plug of wood forming the breech was driven into his chest through the third intercostal space, ½ inch (1.27 cm.) to the right of the sternum. He survived for thirty-seven days. At autopsy the piece of wood was found in the right ventricle. There was no wound of the heart or of the pericardium. On analysis it was believed the piece of wood had entered the superior vena cava and was transported through this vein to the right ventricle.

One case, quoted by Bland-Sutton,[2] originally described by White in 1854, whose description was that of a young soldier who was shot in the left axilla during the "storming of the Great Pagoda, Ragoon" in 1852. He died seventy-two days later from an infection of the left lung and pleural sac. At autopsy a round lead bullet was found in the left ventricle. This bullet apparently had perforated the left lung, passed into a large pulmonary vein and thence to the left ventricle.

Simons (quoted by Schloffer [3]) reported a case of a gunshot wound of the thorax situated over the left sixth intercostal space near the sternum. The bullet entered the inferior vena cava and four days later, at autopsy, was found at the junction of the common iliac veins.

From the Pathological Laboratory of the Cuyahoga County Morgue.

1. Davis, T.: Tr. Prov. M. & S. A. **2**:357, 1834.

2. White, W.: Indian Ann. M. Sc. **1**:289, 1853; cited by Bland-Sutton, J.: Lancet **1**:773, 1919.

3. Schloffer, H.: Beitr. z. klin. Chir. **37**:698, 1903.

Singleton [4] reported a case of gunshot wound in the region of the left breast. At autopsy, fifty-four days later, it was found that the bullet had entered the aorta and apparently had dropped into the left ventricle.

Schmidt [5] reported a case of suicide by shooting in which the bullet entered the chest 10 cm. to the left of the sternum in the sixth intercostal space. It perforated the left pulmonary vein and apparently passed through the left atrium, left ventricle, aorta, right common iliac artery and then through the right external iliac artery to be lodged in the right femoral artery.

Jecks [6] recorded a case of a 36 year old woman who committed suicide by shooting herself twice in the abdomen. One bullet entered just below the xiphoid process and perforated the upper part of the abdominal portion of the aorta. This bullet was found at the bifurcation of the aorta.

Lambotte and Herman (quoted by Schloffer [3]) described a case in which a bullet entered the abdominal portion of the aorta and was found in one of the common iliac arteries.

Dittrich (quoted by Schloffer [3]) reported a case of a gunshot wound of the thorax with perforation of the ascending portion of the aorta. The bullet was found at the bifurcation of the aorta.

In the case reported by Borzéky [7] the bullet entered the right subclavian vein, passed through the superior vena cava, through the right atrium to the inferior vena cava and from there to a large hepatic vein, where it was lodged.

Schloffer [3] added to the medical literature a report of 2 interesting cases in which there was complete clinical recovery from bullet embolism. In one, a case of attempted suicide by an 18 year old youth, the bullet apparently entered the left ventricle of the heart, and twenty-four hours later it embolized the right axillary artery. The patient survived his wound, and the bullet was later surgically removed. In the other case a 17 year old youth was carrying a gun in his right hip pocket. This weapon was accidentally discharged, and the bullet entered the left thigh, penetrated the femoral artery and lodged in the posterior tibial artery. This patient also survived his wound, and the bullet was removed at a later date without serious consequence.

Schloffer cited a case originally reported by Fischer in which a male subject was shot between the scapulas by a shotgun. Some of the lead pellets penetrated the left ventricle of the heart and at autopsy were found in the aorta.

Blumhardt, quoted by Schloffer, reported a case in which a gunshot wound of the chest resulted in a perforation of the left main branch of the pulmonary artery. The bullet was found in the right ventricle. In this case the bullet apparently had dropped against the blood flow from the point of entrance to the point at which it was found.

In a case reported by Tegeler [8] the bullet entered the chest at the level of the seventh intercostal space in the left nipple line and perforated the aorta just above the aortic ring. It then fell into one of the sinuses of Valsalva. The patient recovered from the effects of the wound but died thirteen months later from accidental electrocution. The autopsy revealed the course of the previous gunshot wound.

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4. Singleton, D.: Lancet **1**:33, 1879.
5. Schmidt, G. B.: Zentralbl. f. Chir. **1**:131, 1885.
6. Jecks, C.: Lancet **1**:800, 1890.
7. Borzéky, K.: Beitr. z. klin. Chir. **40**:243, 1903.
8. Tegeler: München. med. Wchnschr. **24**:1740, 1909.

Rubesch [9] reported a case in which a 28 year old man attempted suicide by shooting. The bullet entered the third intercostal space in the left nipple line and was removed from the right femoral artery at operation. It must have entered either the left ventricle or the aorta; from there it moved to the point from which it was removed. This patient, like those reported by Schloffer, completely recovered from the effects of the wound.

Rubesch quoted reports of 3 other cases not mentioned by the foregoing authors. In the first, originally recorded by Bechi and Corsini, there was a gunshot wound of the chest in which the bullet entered a pulmonary vein and was transported to the left ventricle. In the second, reported by Morestin, the bullet entered the right ventricle and then embolized the pulmonary artery. In the third case, originally reported by Hoffmann, the bullet perforated the pulmonary artery and then embolized one of the branches of the pulmonary artery, producing a hemorrhagic infarction of the part of the lung supplied by that artery.

In the case of a soldier wounded in the chest by a piece of shrapnel, reported by O'Neill,[10] the metal entered the left ventricle of the heart, where it was observed by roentgenogram. One-half hour after the roentgen examination, it embolized the left common iliac artery with the result that gangrene developed in the left lower extremity. This patient survived for five days.

Henes [11] observed a soldier who had been shot in the abdomen with a piece of shrapnel. This entered the inferior vena cava and was transported to the right ventricle of the heart, where it was found at autopsy.

Among the cases reported by Bland-Sutton [2] was one in which a piece of shrapnel, 2 cm. square and 1.2 cm. thick, entered the lower portion of the right side of the chest. It penetrated the inferior vena cava and was transported to the right ventricle of the heart. In another case a soldier was wounded in the liver by a piece of shrapnel which penetrated a large hepatic vein. The projectile was transported through the inferior vena cava to the right atrium and then to the right ventricle. In yet another case reviewed by Bland-Sutton the bullet perforated the aorta and then embolized the left external iliac artery.

Bland-Sutton cited 3 other cases of war wounds in soldiers not mentioned by the preceding authors. In each case the metallic projectile was found by roentgenogram to be in a chamber of the heart—in the right atrium, in the right ventricle and in the left ventricle, respectively. On reference to the original articles [12] it was found that the course of the bullet was not described in any instance; therefore it cannot be definitely concluded that the conditions portrayed were truly embolic.

Walcher [13] reported the case of a 38 year old man who was shot 1 cm. to the left of the sternum in the third intercostal space. The bullet entered the anterior wall of the ascending portion of the aorta and then was transported to the left profunda femoris artery. Another case reported by the same author was that of a 6 year old boy who was shot in the left side of the forehead. The bullet entered the longitudinal dural sinus and was transported to the origin of the jugular vein in the right sigmoid sinus.

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9. Rubesch, R.: Beitr. z. klin. Chir. **80**:394, 1912.
10. O'Neill, C. S.: Brit. M. J. **2**:719, 1917.
11. Henes: München. med. Wchnschr. **66**:46, 1919.
12. Lobligeois: Bull. Acad. de méd. **76**:364, 1916. Ledoux-Lebard, R.: J. de radiol. et d'électrol. **1**:35, 1916. Barret, G.: ibid. **1**:37, 1916.
13. Walcher, K.: Zentralbl. f. Chir. **59**:1220, 1932.

Walcher cited 2 cases reported by LeClercq and Muller in each of which the bullet entered the left iliac artery. In the first case the bullet embolized the left profunda femoris artery and in the second the left femoral artery.

Paltauf [14] reported the case of a 21 year old man who was shot in the left third intercostal space. The bullet entered the pulmonary artery and probably dropped into the right ventricle. Seven days later the bullet embolized the right lung. The embolism was designated as the immediate cause of death.

Gonzales [15] reported a case in which a bullet entered the thoracic portion of the aorta and produced embolism in the left iliac artery.

Baker [16] reported the case of a Negro 23 years old, who was shot in the right flank. The bullet entered the aorta 3 cm. above the bifurcation and lodged in the right external iliac artery.

REPORT OF A CASE

A 37 year old Negro was shot in the abdomen during a street fight. He was immediately taken to Charity Hospital. At the time of his arrival, his blood pressure was 40 systolic and 0 diastolic. The gunshot wound was located 5 cm. to the right and 2 cm. above the umbilicus. The patient was given supportive therapy, including an intravenous injection of saline solution. His blood pressure soon rose to 80 systolic and 60 diastolic. Three hours after admission, laparotomy was performed through an incision in the right rectus muscle. Large clots of blood were removed from the peritoneal cavity. Five perforations of the jejunum were sutured. The bullet was not found at operation. As far as could be ascertained, it had traveled through the abdomen to the root of the mesentery. A rubber drain was inserted into the peritoneal sac, the surgical incision was closed and the patient left the operating table in fair condition.

During the following three days a serous exudate and then a frankly purulent exudate drained from the abdomen. The abdomen became distended. The temperature of the patient rose to 105.6 F., and the pulse rate increased gradually to 160 per minute. He died on the third day in the hospital.

An autopsy was performed seventeen hours after death at the direction of the coroner. The immediate cause of death was marked generalized acute sanguineofibrinopurulent peritonitis. The exudate yielded an almost pure culture of Streptococcus. There was also extensive suppurative cellulitis of the abdominal wall regional to the surgical incision. The five perforations of the intestine were well sutured and showed no evidence of leakage. A small defect, about 8 mm. in diameter, closed by a thrombus, was located in the anterior aspect of the right common iliac vein, just below the origin of the inferior vena cava. Extensive examination of the abdominal wall, the lumbar part of the spine, and the abdominal viscera failed to reveal the bullet.

A routine examination of the remaining viscera revealed a "thrombo-embolus" in the left main branch of the pulmonary artery. Closer examination of the "thrombus" showed that it actually consisted of a 32 caliber bullet completely covered by a red blood clot. The clot was firmly adherent to the bullet and slightly adherent to the arterial wall.

In recapitulation, the course of the bullet must have been as follows: After penetrating the anterior abdominal wall and five loops of jejunum, it passed through

14. Paltauf, R.: Wien. klin. Wchnschr. **46**:602, 1933.
15. Gonzales, T. A.: Am. J. Surg. **26**:43, 1934.
16. Baker, R. D.: Am. J. Surg. **29**:282, 1935.

the root of the mesentery to the right common iliac vein just below the inferior vena cava. It apparently passed through the anterior wall of the vein and was stopped at the posterior wall of the vein by the lumbar part of the spine. Excessive bleeding was prevented by the low intravascular blood pressure and the pressure of the surrounding adipose tissue.

Owing to the weight of the bullet and the relatively low intravascular pressure in the common iliac vein, the subsequent course of the bullet would depend in large part on the position of the body after the shot had reached its mark. The record reveals that ten minutes after the shooting the patient was taken in an upright position in a taxicab to a hospital. At this time the pull of gravity undoubtedly caused the bullet to drop into the internal or the external iliac vein as far as the diameter of the vein would permit. Immediately after admission to the hospital, the patient was taken to the operating room. With the body in a prone position, an operation was performed which lasted three quarters of an hour. On being placed in the ward, the patient was kept in shock position for approximately twenty-four hours, i. e., with the head lower than the rest of the body. During this period, the force of gravity would have tended to move the bullet in the direction of the blood flow, and the sucking action of respiratory movements might have aided in the passage of the bullet through the inferior vena cava to the heart. From there it was assisted by the contractions of the right atrium and ventricle in its transit to the left pulmonary artery. On the day after admission, the patient was placed in Fowler's position and kept in that posture until he died, so the bullet could hardly have been transported to the pulmonary artery after the first hospital day. The thrombus, at least in part, may have been deposited on the bullet during its intravascular transportation. The adherence of this thrombus to the wall of the pulmonary artery is further evidence of the deposition of the bullet at that site some time (at least two days according to the history) prior to the death of the patient, Clinically, there was no evidence to suggest that the embolism contributed to death.

COMMENT

Schloffer [3] and Rubesch [9] have attempted to group some of the cited cases of intravascular movement of projectiles into categories depending on whether or not the movement occurred before death and whether or not the intravascular projection was in the direction of the blood stream. This classification appears extremely hazardous, since it would be practically impossible to differentiate objectively between the premortem and the postmortem movement of the projectile from either the clinical or the autopsy observations, especially in those cases in which the subject died soon after being shot. In cases in which the victim of a shooting survives a longer period, it may be possible to show that the transportation of the projectile was premortem by the secondary anatomic alterations which usually accompany the presence of a large foreign body. Evidence of fresh dislocation and movement of the projectile does not necessarily imply that the motion was definitely post mortem.

The intravascular movement of the projectile may be influenced by the force of gravity, the position of the body, muscular and respiratory movements, and to some extent by the force of the blood flow. The

devious pathways taken by the projectiles in some of the cases undoubtedly are explained by an unusual interaction of these forces.

Of extreme interest is the evidence from the case under study and from the previously reported cases that a gunshot wound of the heart or of such large blood vessels as the pulmonary artery or vein, the aorta or the superior or the inferior venae cavae need not result in immediate death or in extensive hemorrhage. In 6 cases there was complete recovery. The fact that loss of consciousness need not supervene immediately and that a person may walk many yards with such an injury, exemplified in the case reported by Davis,[1] is of considerable medicolegal importance to those dealing with related problems.

SUMMARY

A case of bullet embolism of the left main branch of the pulmonary artery following a gunshot wound of the abdomen is described. The literature on projectile embolism is briefly reviewed.

PULMONARY EMBOLISM CAUSED BY LIVER TISSUE

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Pulmonary embolism is a relatively common complication of trauma and is a matter of considerable clinical and medicolegal interest. Certain types of embolism, however, are uncommon. It is the purpose of this report to describe a case of pulmonary embolism due to liver particles, and incidentally to particles of bone marrow, and to make a systematized study of the incidence of this type of embolism among the 1,100 autopsies at the Cuyahoga County Morgue.

REPORT OF A CASE

A 59 year old white woman was struck by an automobile while crossing a street. She was taken to a hospital and pronounced dead within twenty minutes. The duration of life after the injury could not be more closely ascertained. The circumstances of the accident warranted a verdict of manslaughter, and an autopsy, ordered by the coroner, was made two and three-quarter hours after death. The lesions revealed were: numerous abrasions, contusions and ecchymoses of the scalp, face and all four extremities; lacerations of the scalp, the skin of the left ankle and the diaphragm; hemorrhages into the subcutaneous tissues of the scalp; hemorrhages into both pleural sacs and into the peritoneal sac; fractures of the right clavicle, the right radius and ulna, the left tibia, the right pubic bone and the body of the tenth thoracic vertebra; dislocation of the second cervical vertebra with transection of the cervical portion of the spinal cord; fracture of the medial ligaments of the right knee joint with dislocation of the joint; multiple fractures of all ribs except the first three on the left side; laceration of the pericardial sac; focal contusion of the heart; laceration of the endocardium of the right ventricle; multiple lacerations of the spleen; slight subdural and subarachnoid hemorrhages; multiple lacerations and contusions of both lungs, and laceration of the right lobe of the liver.

The laceration of the liver was somewhat unusual in that the capsule was not involved. It was limited to the right lobe; it extended through several large hepatic veins and measured 5 by 4 by 1 cm.

Microscopic examination of the lungs revealed particles of liver in the lumens of several intrinsic pulmonary arteries. These particles varied in size from 50 microns to 2 mm. in the large diameter. The largest piece produced a distention of the artery containing it. At the extreme periphery of this large particle, the cells were distorted beyond recognition. Elsewhere the tissue was well preserved.

From the Pathological Laboratory of the Cuyahoga County Morgue.

The nuclei were well stained. The cytoplasm was granular, and in some of the cells a small amount of brown granular pigment was present. The sinusoidal arrangement could be identified in places. In many areas the tissue appeared compact; the sinusoids apparently were obscured by compression. Spindle-shaped cells suggestive of Kupffer cells could be seen lining some of the sinusoids. In some places there was a suggestion of a distorted central vein. Serial sections failed to reveal a portal area or bile ducts. Conceivably, such emboli might be confused with tissue from the adrenal cortex, but in this instance the adrenal glands were intact; therefore, they could be definitely excluded as a source of the emboli.

One of the sections of lung also revealed a small irregular piece of bone marrow, 100 by 200 microns in diameter, within an intrinsic pulmonary artery. The tissue was composed of a few fat cells separated by clusters of immature cells of the erythropoietic and granulocytic series. No megakaryocytes were noted.

COMMENT

The most common types of pulmonary embolism secondary to trauma are thrombus embolism and fat embolism. The former is due to the dislodgment of a loosely attached venous thrombus, formed, as a rule, regional to the site of trauma. The latter is due to the release of lipoids in a fluid state following fracture of long bones or trauma of a large bed of subcutaneous adipose tissue.[1]

Other forms of pulmonary embolism secondary to trauma are less common. Air embolism has been reported after (1) incision or laceration of the large veins of the neck, (2) attempted abortion by the intrauterine injection of various soapy or antiseptic solutions, (3) injection of air into the urinary bladder or the nasal sinuses for roentgenologic purposes, (4) insufflation of the uterine tubes to determine patency and (5) disengagement of the tubing from the needle in a continuous intravenous injection, permitting air to be sucked into the vein.[2] Embolism caused by a foreign body, e. g., a broken needle or a metallic projectile, has been described; in the former instance it results from the migration of a fragment of needle lost below the skin surface,[1a] and in the latter it occurs as a consequence of a gunshot wound with a lead bullet or a piece of shrapnel coming to rest within a vascular space.[3]

Pulmonary emboli of tissue other than blood or fluid lipoids are rare. The most familiar of these are pieces of bone marrow found after multiple fractures of bones.

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1. (*a*) Karsner, H. T.: Human Pathology, ed. 4, Philadelphia, J. B. Lippincott Company, 1935. (*b*) Gonzales, T. A.; Vance, M., and Helpern, M.: Legal Medicine and Toxicology, New York, D. Appleton-Century Company, Inc., 1937.

2. Deadman, W. J.: Canad. M. A. J. **37**:157, 1937. Karsner.[1a] Gonzales and others.[1b]

3. Straus, R.: Arch. Path., this issue, p. 63.

A pulmonary embolus containing brain tissue following trauma to the head has been reported but is extremely rare.[4]

Pulmonary emboli of liver are also rare but have been seen in cases of hepatic necrosis.[1] Cases of hepatic embolism of the lungs as a complication of trauma were first described independently by Jurgens and by Recklinghausen in 1886 (quoted by Schmorl[5]). Schmorl described 2 cases and Zenker[6] an additional case. In 1935 Willer[7] summarized the literature and reported another case. In most of the preceding cases some of the liver particles in the pulmonary artery could be grossly identified. In the case described by Zenker the hepatic embolism of the lung followed a gunshot wound of the liver; in the others it followed blunt trauma.

Among 1,100 autopsies at the Cuyahoga County Morgue there were 104 cases of injury to the liver in the form of gunshot wounds, stab wounds and lacerations caused by blunt trauma. In 40 of these cases the liver was severely lacerated. The original lung sections were reexamined, and in the 40 cases in which the liver was severely lacerated numerous additional sections of the lungs were made. In all instances they were examined for the specific purpose of detecting the presence of liver emboli, but such emboli were found in only the single case. However, it is recognized that random sections from various parts of the lungs represent an extremely small portion of the parenchyma. Thus it can hardly be said that the systematic reexamination of the lung sections and the examination of additional sections definitely excluded the presence of liver emboli, but at least the result supports the contention that, if present, such emboli were not as profuse as in the case reported in this article.

SUMMARY

A case of pulmonary embolism caused by lodgment of liver particles is described, the only case encountered in 104 autopsies on persons with mild to severe injury of the liver.

4. Krakower, C.: Arch. Path. **22**:113, 1936.
5. Schmorl, G.: Deutsches Arch. f. klin. Med. **42**:409, 1888.
6. Zenker, F. A.: Deutsches Arch. f. klin. Med. **42**:505, 1888.
7. Willer, H.: Centralbl. f. allg. Path. u. path. Anat. **62**:209, 1935.

Case Reports

FIBROLEIOMYOMA OF THE BREAST

ROBERT J. STEIN, NEWPORT, VT.

Primary fibroleiomyoma originating in the breast parenchyma independent of the nipple is a pathologic rarity. Up to 1940 only 4 authentic cases had been described in the literature (Lebowich and Lenz [1]). Strong [2] was the first to describe such a tumor of the breast proper, which was diagnosed as leiomyoma and had a microscopic structure suggesting its origin from the tunica media of the blood vessels. Lieber [3] described 3 cases of primary fibromyoma of the breast, in 1 of which the tumor originated from the parenchyma; in the other 2 it originated from the nipple. Recently Melnick,[4] and Lebowich and Lenz [1] described a number of cases of primary fibromyoma originating in the breast proper.

Although Cheatle and Cutler [5] do not mention this type of tumor in their monograph and Driak and Sternberg [6] doubt the occurrence of true parenchymal fibromyoma, I wish to present a case of tumor of the breast proved histologically to be fibroleiomyoma.

REPORT OF A CASE

A white woman 54 years of age was admitted to the hospital service of Dr. C. G. Schurman and Dr. W. H. McBride, complaining of a mass in the right breast. This mass was first observed twenty-six years before, after a miscarriage, and in the past nine years it had increased in size. Owing to the size of the tumor and to the discomfort caused by it, the family physician advised a mastectomy.

The patient was well developed and in perfectly good health. The laboratory investigation, including the Wassermann and the Eagle test, gave negative results.

The right breast was enlarged and contained large, firm, circumscribed, freely movable masses in the medial upper quadrant. The nipple appeared normal and was not connected to the tumor mass in any fashion. The axillary and supraclavicular lymph nodes were not palpable.

With the patient under ether anesthesia, a radical mastectomy was done. The convalescence was uneventful, and the patient was discharged ten days after admission to the hospital.

From the Pathological Laboratories, Orleans County Memorial Hospital.

1. Lebowich, R. J., and Lenz, G.: Am. J. Cancer **38**:73, 1940.

2. Strong, L. W.: Am. J. Obst. **68**:53, 1913.

3. Lieber, K.: Beitr. z. path. Anat. u. z. allg. Path. **60**:449, 1915.

4. Melnick, P. J.: Arch. Path. **14**:794, 1932.

5. Cheatle, G. L., and Cutler, M.: Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, Philadelphia, J. B. Lippincott Company, 1931.

6. Driak, F., and Sternberg, H.: Deutsche Ztschr. f. Chir. **207**:352, 1928.

The cut surface of the breast exhibited a number of nodules which cut with great resistance. The largest measured 4 by 3 cm. (fig. 1). The tumor masses were grayish white; the cut surface projected well beyond that of the fat and appeared striated and concentric. The tumor stroma was studded throughout with areas of calcareous deposit. The areola and nipple were normal in appearance and not attached to the tumor masses, and there was no gross evidence of neoplastic infiltration.

Serial microscopic sections of the tumor were stained with hematoxylin and eosin, Van Gieson's stain, Mallory's triple stain and Wilder's reticulum stain.

The sections consisted of interlacing bundles arranged in an irregular fashion. The bundles were composed of two different tissue elements, mingled together in varying proportions, and all were more or less closely packed. The Van Gieson

Fig. 1.—Tumor masses exhibiting projection of their cut surfaces beyond the fat and the striation of the stroma.

and the Mallory triple stain brought out the fibrous elements as well as the smooth muscle fibers. The muscle fibers appeared somewhat thicker than normal; the cytoplasm was moderately granular; the nuclei stained hyperchromatically and appeared larger and rod shaped with blunt ends. The nuclei of the connective tissue cells also appeared hypertrophied but were narrower and shorter, with pointed extremities (upper part of fig. 2).

Adjacent to the interlacing bundles of connective tissue and muscle fibers were areas of undifferentiated mesenchymal cells. These cells appeared irregular or stellate shaped and were connected with one another by their thin protoplasmic processes (lower part of fig. 2). Dispersed throughout the sections were a number of lymphocytes and plasma cells.

Surrounding the tumor mass proper was a connective tissue capsule which separated it from the normal breast tissue.

From the structural arrangement of the cellular elements and the absence of infiltration of the tissue this tumor must be considered a benign neoplasm of mesodermal origin.

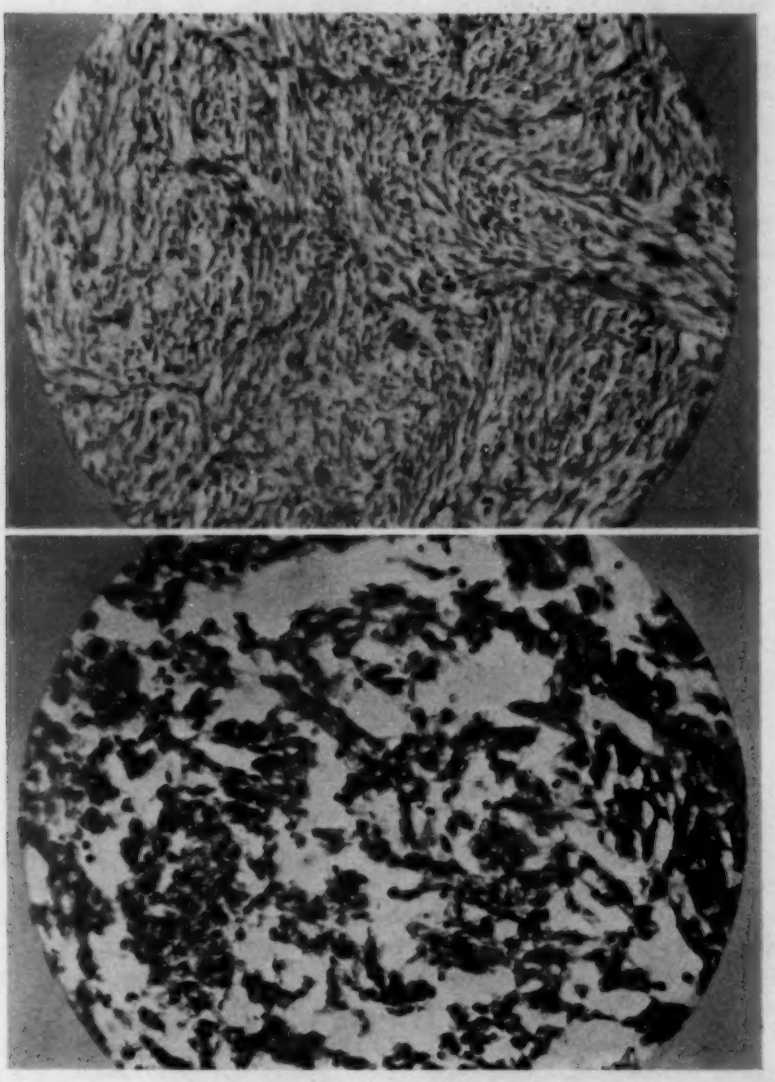

Fig. 2.—Upper part: a representative area exhibiting the interlacing bundles of the connective tissue and smooth muscle fibers. Lower part: undifferentiated mesenchymal cells forming a syncytium by means of their protoplasmic processes.

SUMMARY

Another case of primary parenchymal fibromyoma of the breast is reported. The tumor was of twenty-six years' duration and painless. It had no connection with the nipple.

SITUS INVERSUS OF THE SUPERIOR VENA CAVA

BÉLA HALPERT, M.D., NEW ORLEANS

Anomalies of the large venous trunks in the upper part of the thorax have been observed in newborn infants, in children and in adults. According to Beattie,[1] they may occasionally be of importance in the roentgenographic diagnosis of thoracic conditions. A complete list of the reports of such anomalies has been recently compiled by Chouke.[2]

The rarest of these anomalies is the transposition of the superior vena cava and its tributaries so that they present a mirror image of the normal. In such situs inversus of the superior vena cava, the right superior vena cava is absent, and the left superior vena cava empties at the site where usually the oblique vein of the left atrium (Marshall) joins the coronary sinus. The rarity of a complete situs inversus of the superior vena cava is indicated by the fact that in 1930 only about 18 cases could be assembled.[3] To this the case of Schmidt (cited by Atwell and Zoltowski [4]) should be added. Since then authentic cases have been reported by Beattie,[1] Atwell and Zoltowski [4] and Wallraff,[5] bringing the total to 22. In this paper an additional case, the second which I have observed, is presented. The anomaly occurred in a newborn Negro girl, who died of intracranial hemorrhage from tears in the tentorium cerebelli twelve hours after birth.

REPORT OF A CASE

The child was born at the estimated ninth month of pregnancy. The duration of labor was about fourteen hours. The position was frank breech. At birth the heart sounds were weak and the respirations poor. The child was kept in an oxygen tent but remained cyanotic and died twelve hours after birth.

At necropsy the child appeared well proportioned and fairly well nourished, was 44 cm. tall and weighed 2,000 Gm. The skin was white. The scalp was covered with scant delicate blond hair. There were no anomalies of the ears, nose and mouth. The neck, chest and abdomen were well shaped. The external genitals appeared edematous. No changes were noted over the back. The upper and lower extremities were proportionate. There was a deformity of the left wrist and an accessory little finger, 2 cm. long, attached by a thin pedicle to the left little finger.

Five centimeters of moist cord was attached to the umbilicus. No changes were noted about the umbilical vessels and the remains of the urachus. The small

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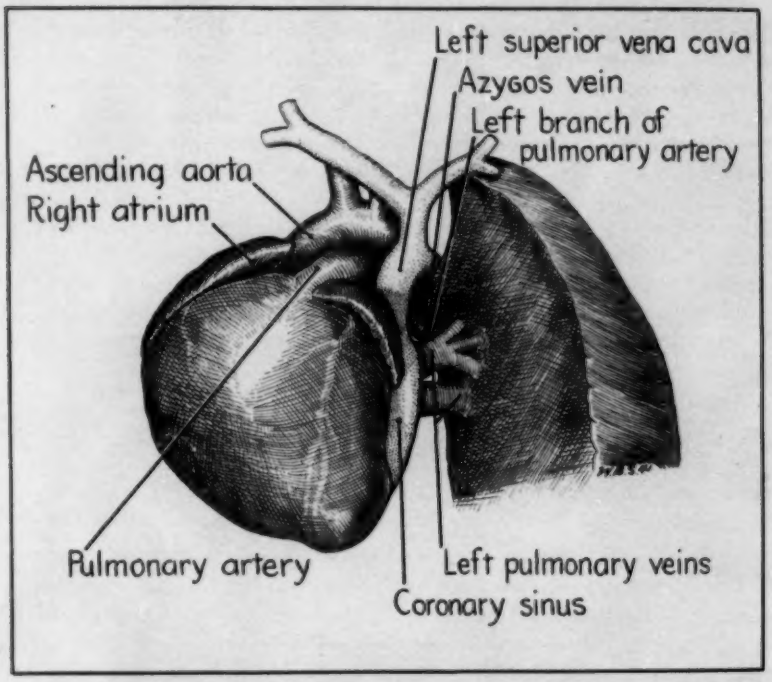
From the departments of pathology and bacteriology of the Charity Hospital of Louisiana at New Orleans and the Louisiana State University School of Medicine.

1. Beattie, J.: Canad. M. A. J. **25**:281, 1931.
2. Chouke, K. S.: Anat. Rec. **74**:151, 1939.
3. Halpert, B., and Coman, F. D.: Am. J. Path. **6**:191, 1930.
4. Atwell, W. J., and Zoltowski, P.: Anat. Rec. **70**:525, 1938.
5. Wallraff, J.: Anat. Anz. **87**:305, 1939.

intestine, the cecum and the ascending colon were suspended on a common mesentery. About 40 cm. proximal to the ileocecal valve there was a finger-like projection from the free margin of the ileum, 2 cm. long, representing Meckel's diverticulum.

There were no ossification centers in the sternum. The costochondral junctions were straight. The thymus gland was 3.5 by 3 by 1 cm. No changes were noted on its cut surfaces. The pleural cavities showed no excess of fluid; their surfaces were smooth and glistening.

There was no excess of fluid in the pericardial cavity; the surfaces were smooth and glistening. The heart measured 5 cm. from base to apex and 4 cm. across



Situs inversus of the superior vena cava in a newborn Negro girl. There is no trace of a right superior vena cava. The left superior vena cava empties into the coronary sinus. The course of the tributaries of the superior vena cava and of the innominate and azygos veins presents a mirror image of the normal.

the base. The apex was rounded, and all the chambers appeared distended. The transverse diameter of the heart was 6 cm., and that of the thorax was 8 cm. There was no superior vena cava on the right (figure). A left superior vena cava, of the caliber usual for the right, joined the coronary sinus, which was proportionately enlarged and after its usual course emptied into the right atrium. No other anomalies were noted in the course or the arrangement within the pericardial cavity of the inferior vena cava, the pulmonary veins, the aorta, the pulmonary artery or the coronary arteries. The tributaries of the coronary sinus were as

usual except for the absence of the oblique vein of the left atrium (Marshall). The course of the tributaries of the superior vena cava and of the innominate and azygos veins presented a mirror image of the normal.

Both lungs were air containing in their anterior portions and dark red and seemingly not air containing in their posterior portions. No changes were noted in the liver, gallbladder, extrahepatic biliary ducts, pancreas or spleen. The adrenal glands were of the usual size and appearance. The right kidney seemed enlarged, and its pelvis and ureter were markedly distended. The latter was tortuous, thin walled and enlarged to the size of the small intestine. No changes were noted in the left kidney or in the urinary bladder. There were no anomalies of the inferior vena cava or of its tributaries. The abdominal aorta was in its usual position. The uterus, fallopian tubes and ovaries were delicate, proportionate and symmetric.

The anterior fontanel was 3 by 5 cm.; the posterior fontanel was closed. The leptomeninx was delicate and transparent. The cerebral and cerebellar hemispheres, the cerebral peduncles, the pons and the medulla oblongata were proportionate and symmetric. No areas of hemorrhage or of softening were noted in the brain substance proper, nor was there any extravasation of blood into the cavities of any of the ventricles. There was a tear in the tentorium cerebelli on each side with extravasation of blood into the posterior cranial fossa. The hypophysis was of the usual size and appearance. The superior sagittal sinus emptied into the left transverse sinus. No other anomalies were noted in the venous sinuses of the dura mater.

COMMENT

In no report of a case prior to my own was any mention made of the course of the superior sagittal sinus. Whether the emptying of this sinus into the left transverse sinus is the cause of the transposition or only a part of it still remains to be determined. The case herein recorded is remarkable also because of the additional developmental anomalies.

SUMMARY

A rare vascular anomaly, transposition of the superior vena cava and its tributaries, is reported in a newborn Negro girl, who in addition had the following developmental anomalies: right hydroureter and hydronephrosis, diverticulum of the ileum, mesenterium commune, deformity of the left wrist and accessory left little finger.

LYMPHANGIOENDOTHELIOMA OF THE UTERUS

JOSEPH A. TUTA, M.D., PH.D., CHICAGO

True lymphangiomatous tumor of the uterus, like that of the fallopian tube and the ovary, is very rare. Dorland,[1] in 1916, made a comprehensive review of the subject and discussed the complex relationships between peritheliomatous and endotheliomatous tumor formation. More recently, Löffler [2] reported a case of lymphangioma of the uterus and emphasized the rarity of the tumor. He stated that neither Meyer [3] nor Kaufmann [4] had ever studied a case in which the diagnosis was free from criticism and that in the material of the Vienna hospitals there was no example of true lymphangioma of the uterus.

REPORT OF A CASE

A housewife 45 years of age was admitted to the Grant Hospital with a complaint of pain in the lower left quadrant of the abdomen. The pain radiated down the left leg, and she stated that she had experienced a similar attack one month before. Several days before entering the hospital she was nauseated and vomited. The menstrual periods had been irregular for three years, occurring at two to three month intervals. She had 4 children, and there was no history of miscarriages. Supracervical hysterectomy and bilateral salpingo-oophorectomy were done by Dr. Ernest Spieler, who permits me to report the case. A large parovarian cyst was also removed from the left side.

The uterus measured 75 by 65 by 60 mm. The myometrium varied in thickness up to 28 mm. There was an intramural fibromyoma, 8 mm. in diameter, the cut section of which was pale tan and fasciculated. There was also a subserous fibromyoma, 15 mm. in diameter. The endometrium was purple-red and averaged 5 mm. in thickness. There was a submucous nodule at the fundus of the uterus, measuring 14 mm. in diameter and protruding slightly into the uterine cavity. The cut surface was pale yellow and moderately firm, and the central portion had a slightly pitted appearance. The left fallopian tube projected over the upper surface of a parovarian cyst. The cyst measured 12 by 10 by 8.5 cm. and contained clear fluid. The surface of the cyst was dark purple-red, and the blood vessels were prominent. The inner lining was purple-red and smooth.

From the Grant Hospital and the Department of Pathology of the University of Illinois College of Medicine.

1. Dorland, W. A.: Surg., Gynec. & Obst. **26**:576, 1916.

2. Löffler, E.: Zentralbl. f. Gynäk. **59**:2888, 1935.

3. Meyer, R., in Veit, J.: Handbuch der Gynäkologie Herausgegeben von W. Stoeckel, ed. 3, Munich, J. F. Bergmann, 1931, vol. 6, pt. 1; in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1930, vol. 7, pt. 1.

4. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 8, Berlin, Walter de Gruyter & Co., 1929, p. 1301.

The left ovary contained a cyst, 2.5 cm. in diameter, the lining of which was purple-gray. The fimbriated end of the right fallopian tube was patent, and the mucosa was purple-gray. The right ovary measured 30 by 20 by 10 mm., and the cut surface was pale yellow.

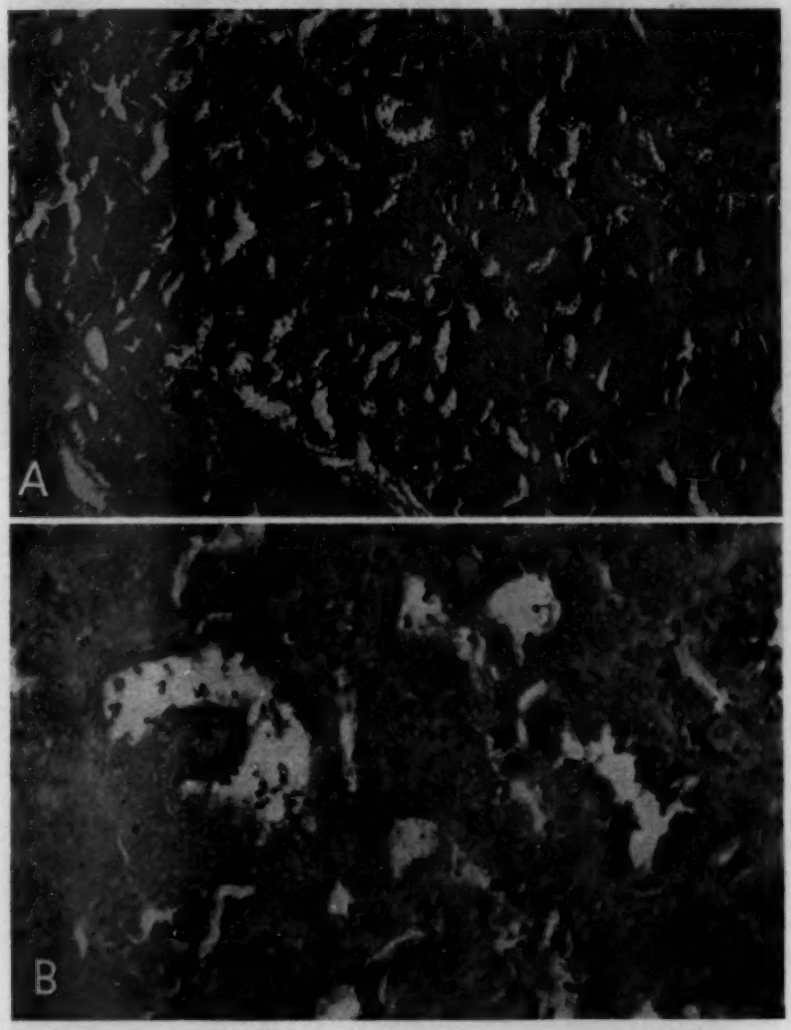


Fig. 1.—*A*, central portion of the tumor nodule. There are numerous irregular lymphatic spaces. Hemalum-eosin; × 80. *B* shows that many of the irregular lymphatic spaces are surrounded by wide collars of proliferating endothelial cells. Similar cells are seen in the stroma. Lymphoid cells are present in some of the channels. Hemalum-eosin stain; × 140.

The submucous tumor was composed of numerous irregular empty spaces, some of which were lined by a single layer of flattened endothelial cells. In certain areas there were numerous small spaces which appeared to radiate away

Figure 2

(See legend on opposite page)

from the larger endothelial-lined structures. Some of these smaller structures showed one or two flattened endothelial cells in the lumen. Two or three lymphoid cells were seen filling some of the smaller spaces. Many of the spaces were lined by several layers of cells, leaving the lumen consisting only of a central irregular slitlike space. These cells possessed large vesicular nuclei of round or oval shape. The nuclear chromatin content was sparse. In some of the vesicular nuclei there were several minute nucleoli; others had no visible nucleoli. Some of the nuclei had a single small slightly eosinophilic nucleolus. In a few of the spaces the coexistence of the flattened endothelial cells and proliferating cells with larger vesicular nuclei gave evidence of a transitional state and suggested an intimate relationship between the flattened endothelium and the more undifferentiated proliferative endothelial cells. Along with the proliferation of cells into the lumen there appeared to be an outward growth of similar cells into the stroma. In areas the stroma was very cellular and contained many cells with round vesicular nuclei.

Weigert's elastic tissue stain showed the stroma to be composed chiefly of a dense network of coarse and fine branching elastic fibers. A few fine fibers extended into the structures made up of several layers of cells having a small irregular cavity in the center. The blood vessels in the adjacent myometrium contained many elastic fibers in their walls. The connective tissue elements of the myometrium other than the blood vessel walls did not show elastic fibers. The tumor nodule stained pale yellow with Van Gieson's stain. There were a few visible coarse irregular branching fibers which stained pale brown but did not stain red as did the connective tissue of the adjacent myometrium. The Perdrau silver stain for reticulum showed numerous interlacing coarse and fine argyrophilic fibers. The tumor tissue did not take the mucicarmine stain. Masson's[5] trichrome method revealed moderate numbers of coarse branching fibers. Mallory's phosphotungstic acid–hematoxylin stain showed a moderate number of coarse yellow-staining fibers. An occasional bundle of smooth muscle fibers was found toward the periphery of the tumor nodule near the junction of the tumor and the myometrium. The tumor nodule did not have a definite capsule but stopped rather abruptly at the junction with the surrounding uterine musculature. In a few places along its circumference the neoplastic tissue blended more gradually into the adjacent myometrial tissue. Several sections taken from other portions of the uterus showed no trace of lymphangiomatous structures. The uterine mucosa showed glandular cystic hyperplasia. The left fallopian tube and parovarian cyst presented extensive hemorrhagic infiltrations.

5. Masson, P.: J. Techn. Methods **12**:75, 1929.

EXPLANATION OF FIGURE 2

A, large cells with round and oval vesicular nuclei forming many layers around the lymphatic spaces, protruding into the lumen of the irregular channels and extending into the stroma. Hemalum-eosin stain; × 450.

B, lymphatic channels lined on one side by flattened endothelium and on the opposite side by large proliferating endothelial cells. Hemalum-eosin stain; × 450.

C, large numbers of elastic fibers and masses of proliferated endothelial cells. Weigert's elastic tissue stain; × 140.

COMMENT

The problem of first consideration in the classification of a lymphangiomatous tumor of the uterus is to eliminate the possibility of lymphangiectasis in preexisting fibromyoma. The extreme degree of endothelial proliferation seen in this tumor is not present in the usual lymphangiectatic formation found in uterine fibromyoma. Mallory's phosphotungstic acid–hematoxylin stain revealed no smooth muscle bundles in the greater portion of the tumor. A few fibers were recognized at the periphery and at the junction with the adjacent myometrium. This gave conclusive evidence that the lymphatic elements were not engrafted on old fibromyoma. Red-staining connective tissue fibers were not seen when sections were stained by the method of Van Gieson.

Weigert's elastic tissue stain showed the stroma surrounding the lymphatic spaces to be composed of large numbers of fine and coarse elastic fibers. In the tumor described by Löffler,[2] a similar marked production of elastic tissue was found. Löffler [2] suggested that this finding was in favor of a neoplastic formation of lymphatic structures rather than a metamorphosis of preexistent lymphatic vessels. Before any significance can be attached to the large amount of elastic tissue found in the tumor, one must take into account the age and the parity of the patient. In the lymphangioma of the fallopian tube reported by Sanes and Warner,[6] most of the fibers in the stroma were reticular and elastic in character.

Ewing [7] considered the subject of endothelioma in great detail. A lymphangiomatous tumor has an organoid structure, the neoplastic process consisting of endothelial elements and the supporting connective tissue. In the tumor reported in this paper there was proliferation of endothelial cells with the formation of lymphatic channels as well as an extensive development of elastic fibers. There was an outward proliferation away from the channels, giving the stroma in places a very cellular appearance. Any attempt to determine the origin of endotheliomatous tumors meets with difficulties. Whether they are derived from the lining endothelial cells or the so-called perithelial cells is a matter of conjecture. The transitions and intimate relationship between the more differentiated flattened endothelial cells lining the irregular channels in the tumor and the more undifferentiated larger cells with round or oval nuclei in the same channel can be followed in the microscopic sections. The areas of extreme endothelial proliferation justify the use of the term "lymphangioendothelioma," in contrast to the term "lymphangioma," which is generally used for tumors composed of lymphatic spaces having little or no proliferating endothelium.

There was no definite capsule or reaction surrounding the tumor nodule. This is in accord with angiomatous tumors in general. The finding of a few lymphocytes in some of the channels in the tumor indi-

6. Sanes, S., and Warner, R.: Am. J. Obst. & Gynec. **37**:316, 1929.

7. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, pp. 335-385.

cates some communication with the lymphatic channels outside of the tumor proper. This is not contrary to the findings in some cases of true lymphangioma, according to Ewing.[7]

In spite of the lack of invasion and the rather abrupt line of demarcation between the tumor and the uterine musculature, the endothelial proliferation indicates that the tumor histologically possessed the potentiality of becoming invasive and eventually producing metastases.

SUMMARY

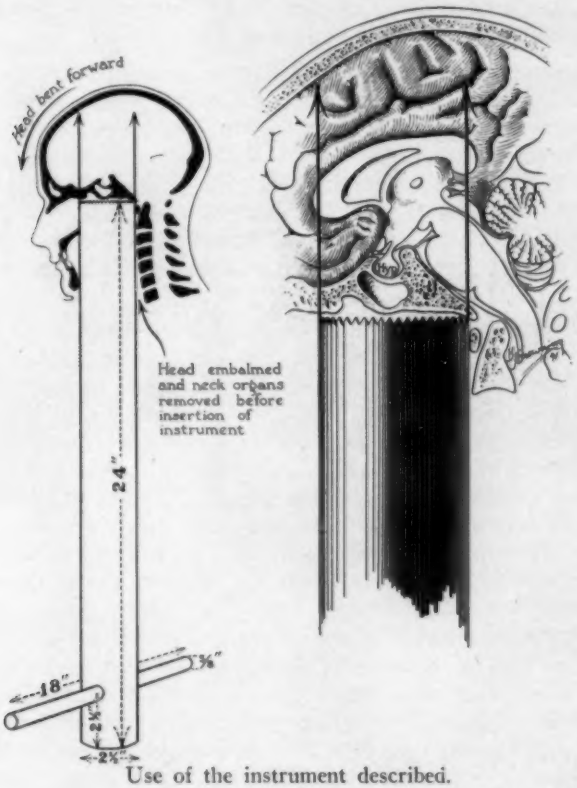
A case of lymphangioendothelioma of the uterus is reported. The neoplasm was characterized by endothelial proliferation with formation of irregular lymphatic channels and by the presence of a large amount of supporting elastic tissue. Special stains rule out the possibility of a lymphangiectatic process in preexisting fibromyoma.

Laboratory Methods and Technical Notes

AN INSTRUMENT FOR OBTAINING THE HYPOPHYSIS AND A PORTION OF THE BRAIN WITHOUT REMOVING THE CALVARIUM

RICHARD H. FOLLIS JR., M.D., BALTIMORE

Frequently permission to examine the cranial contents at autopsy is not obtained. The usual reason given is that the marks of the incision



Use of the instrument described.

will show and the head will thus be disfigured. Failure to examine the brain detracts from the proper interpretation of observations at many autopsies. Then, too, there are less common instances in which an examination of the hypophysis is greatly to be desired.

Although a portion of the contents of the cranial cavity can be removed after the bone at the base of the skull has been chiseled away,

From the Department of Pathology, Johns Hopkins Medical School.

the operation is a time-consuming one. The instrument described here was devised to make removal of a portion of the brain and the hypophysis an easier procedure.

DESCRIPTION OF INSTRUMENT

This instrument is made from a piece of hardened steel pipe 24 inches (60.96 cm.) long, 2½ inches (6.35 cm.) in diameter and 3/16 inches (0.48 cm.) in thickness. Saw teeth are cut at one end and this end tapered down to a thickness of 1/16 inch (0.16 cm.). Two holes 5/8 inches (1.59 cm.) in diameter are cut 2½ inches from the opposite end so that a steel rod 18 inches (45.7 cm.) in length can be passed through them to act as a handle.

After the abdominal and thoracic viscera have been removed, the upper extremities and the head are embalmed through the great vessels. The neck organs, including the tongue, are then removed in toto by sharp dissection. The instrument is inserted into this space and pushed up along the vertebral bodies until its teeth are in contact with the base of the skull (figure). The head is held firmly by an assistant, and the tube is rotated vigorously back and forth with the handle while being pressed constantly on the base of the skull. The bone is sawed through and the instrument is pushed into the cranial cavity until it reaches the calvarium. After several light rotary motions, it is withdrawn containing a cylinder of brain tissue, the sella turcica and hypophysis, the posterior air sinuses and the sphenoid bone. The defect is packed with cotton or oakum; the nares are similarly plugged.

An instrument of the diameter given here is suitable only for adults. A smaller one can be made to be used in children. In this department of pathology, the removal of a good-sized portion of the brain together with the hypophysis has proved a relatively easy procedure in cases in which permission to open the head in the usual way was not obtained.

TECHNIC FOR SECTIONING SOFT BONES AND HARD TISSUES BY CELLOIDIN AND PARAFFIN METHODS

MORRIS KOLIN, B.S., NEW YORK

Many difficulties are encountered in cutting sections in the ordinary routine procedures of fixation and embedding of soft bones and hard tissues. With soft bones, part of the lime salts have to be removed; with hard tissues, successful sectioning depends solely on fixation and embedding.

The following procedures are recommended for the fixation and embedding of tissues in celloidin and paraffin.

CELLOIDIN METHOD

1. Fix sections 2-5 mm. thick in a 4 per cent solution of chemically pure formaldehyde for twenty-four hours.

2. Wash in water for three to four hours.

3. Place in a 5 per cent solution of chemically pure glacial acetic acid ($CH_3.COOH$ in a concentration of 99.8 per cent in distilled water) for twenty-four hours or longer.

4. Wash in distilled water for twenty-four hours.

5. Dehydrate in 80 per cent alcohol for one hour.

6. Treat with acetone ($(CH_3)_2CO$—American Chemical Society's specifications—for one hour.

7. Treat with oil of clove U. S. P. for three to six hours.

8. Embed for twenty-four to forty-eight hours in an 8 per cent solution of purified pyroxylin in equal parts of ether and absolute alcohol (celloidin).

9. Embed for twenty-four to forty-eight hours in a 12 per cent solution of purified pyroxylin in equal parts of ether and absolute alcohol (celloidin).

10. Cut sections approximately 8 microns in thickness.

11. Place sections in 80 per cent alcohol and rinse in distilled water.

12. Stain with Ehrlich's or Harris' hematoxylin for five to fifteen minutes.

13. Wash in distilled water for several minutes.

14. Place in acid alcohol (1 per cent hydrochloric acid in 70 per cent alcohol) until the celloidin is colorless and the tissue is medium rose in color.

15. Wash in distilled water.

16. Add a few drops of stronger ammonia water U. S. P. or 20 drops of a saturated solution of lithium carbonate per hundred cubic centimeters of distilled water. Keep sections in this solution until the tissue turns blue; this should occur within a few seconds.

17. Wash thoroughly in distilled water.

From the Office of the Chief Medical Examiner.

18. Flood the section with a 1 per cent aqueous solution or a 1 per cent alcoholic solution of eosin diluted 1:6, for thirty seconds to one minute.

19. Pass through 95 per cent alcohol—two changes—and transfer to a slide. Blot with filter paper and clear in oil of thyme or oil of bergamot N. F. for five minutes. Again blot with filter paper and mount in neutral balsam.

NOTE.—For the acetone and oil of cloves mentioned in steps 6 and 7 can be substituted 95 per cent alcohol and absolute alcohol–ether for one hour each.

PARAFFIN METHOD

1. Fix sections 2-5 mm. thick in a 4 per cent solution of chemically pure formaldehyde for twenty-four hours.

2. Wash in water for three to four hours.

3. Place in a 5 per cent solution of chemically pure glacial acetic acid (CH_3COOH in a concentration of 99.8 per cent in distilled water) for twenty-four hours or longer.

4. Wash in distilled water for twenty-four hours.

5. Dehydrate in 80 per cent alcohol, then in 95 per cent alcohol, then in absolute alcohol, twelve hours each.

6. Treat with chloroform for one and one-half hours, then with ⅓ chloroform and ⅔ paraffin in an oven at 52 C. for two hours.

7. Immerse in pure melted paraffin for two hours.

8. Embed in paraffin and cut sections 7 microns in thickness.

9. Deparaffinize: Place in xylene three times, five minutes each—to take out paraffin.

10. Place in 95 per cent alcohol three times, five minutes each, to take out xylene.

11. Wash well in two changes of water to take out alcohol.

12. Stain with Harris' hematoxylin for five to fifteen minutes.

13. Wash in distilled water for several minutes.

14. Place in acid alcohol (1 per cent hydrochloric acid in 70 per cent alcohol) until tissue is medium rose in color.

15. Wash in distilled water.

16. Add a few drops of concentrated ammonia (28 per cent) in distilled water. Keep sections in this solution until tissue turns blue; this should occur within a few seconds.

17. Wash thoroughly in distilled water.

18. Flood section with an alcoholic solution of erythrosin (1 part of saturated alcoholic solution of erythrosin to 2 parts of 95 per cent alcohol) for thirty seconds to one minute.

19. Place in 95 per cent alcohol, two changes, then in absolute alcohol, then in xylene, three changes, and mount in gum dammar.

NOTE.—The use of glacial acetic acid is of the utmost importance in both the celloidin and the paraffin methods to obtain sharp nuclear staining, to soften hard tissues and bones by removing lime salt deposits and in order to prevent swelling and maceration of the tissue.

Cleanliness is essential—all glassware should be cleaned in a potassium dichromate–sulfuric acid mixture.

Distilled water should be used for all preparations.

The staining solutions should be filtered immediately before use.

General Reviews

MYOCARDITIS

A GENERAL REVIEW, WITH AN ANALYSIS OF TWO HUNDRED AND FORTY CASES

OTTO SAPHIR, M.D.
CHICAGO

(Concluded from page 1050)

MYOCARDITIS ASSOCIATED WITH INFECTIOUS GRANULOMAS

Tuberculosis.—Horn and Saphir in 1935 reviewed the literature on tuberculous myocarditis. Three main types were differentiated, namely, the nodular, the miliary and the diffuse infiltrative types. The last should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis or if the tubercle bacillus can be demonstrated either by inoculation of guinea pigs or by staining methods. Otherwise this form of tuberculosis cannot be differentiated from the so-called specific productive myocarditis (Saltykow). For similar reasons it is difficult to attribute a tuberculous origin to fibrous myocardial lesions which may be present in the hearts of subjects dying of tuberculosis. Hence the term "chronic interstitial tuberculous myocarditis" should be discarded. Horn and Saphir also reported 3 cases of miliary tuberculosis of the myocardium, in 1 of which a conglomerate tubercle was revealed. The patients were children. The literature also discloses that the greater percentage of myocardial miliary tubercles occurred in children. They stressed that this may indicate that the finding of miliary tubercles in the hearts of young subjects who died of miliary tuberculosis is attended with less difficulty because of the relatively larger areas of myocardium examined histologically.

Auerbach and Guggenheim also reviewed the pertinent literature and reported 6 additional cases of tuberculosis of the myocardium. In one of these tuberculoma was found in the right auricle, and in another, in the right ventricle. Albert found in 2 hearts miliary tubercles in addition to lymphocytic infiltrations. Such infiltrations were also found in the hearts of tuberculous children in the absence of tubercles.

Castex and de Elizalde reported a very unusual case of possible tuberculous myocarditis. There was no evidence of tuberculosis in the lungs, but tuberculosis was encountered in the mediastinal nodes. The heart weighed 500 Gm. The myocardium of the right ventricle

contained many tubercles which extended into the endocardium. Tubercle bacilli were not described in the myocardium. Clinically, this myocarditis was called "primary myocarditis."

Yamada recently quoted Masugi, who apparently observed what was interpreted as a transition from typical rheumatic granuloma to "rheumatoid" granuloma and "tuberculoid" granuloma, inferring a possible relationship between rheumatic fever and tuberculosis. Yamada in collaboration with Takeda and Simpo (see Yamada) found granulomatous lesions in the hearts of 39 of 350 patients with tuberculosis. These consisted principally of fibrohistiocytic elements and a few lymphocytes, polymorphonuclear leukocytes and fibroblasts. These lesions classed as granuloma were divided into those which very closely resembled Aschoff bodies (2 instances), those in which fibrohistiocytic cells revealed a marked basophilic cytoplasm and which only somewhat resembled Aschoff bodies (14 cases), and those which were different from Aschoff bodies. The cells comprising these structures had scanty basophilic cytoplasm and obscure nuclei and showed transitions to epithelioid cells (23 instances). They were found entirely in the interstitial tissue, particularly in the perivascular connective tissue. In 9 instances true tubercles were also present. The hearts of 13 of 120 patients who died of acute infectious diseases revealed lesions, diagnosed as granuloma, which somewhat resembled the granuloma seen in tuberculosis. It was stressed that in 3 hearts taken from patients who died as a result of lobar pneumonia changes were present resembling more those seen in hearts involved in rheumatic fever than those described in tuberculosis. The conclusion was reached that the granuloma found in tuberculosis is the result of allergy to tuberculosis.

Wuhrmann also expressed the opinion that there is a nonspecific form of tuberculous myocarditis, a diffuse interstitial lesion not showing tubercle bacilli. Myocarditis was found in 15 patients who died from various forms of tuberculosis; it was characterized by infiltrations of round cells, polymorphonuclear leukocytes and a few eosinophilic cells. Miliary tubercles were also occasionally encountered in the myocardium. He held that the diffuse interstitial myocarditis in tuberculosis is also of tuberculous origin. This belief was based on experiments performed on rabbits. The testes of these animals were inoculated with the bovine type of tubercle bacilli. Twenty-one days later the same doses of the same culture material were injected intravenously. In these rabbits he observed inflammatory myocardial changes which were similar to those seen in the tuberculous patients.

Šikl (1933) stressed that it was surprising how seldom tubercle bacilli had been found in miliary tuberculous myocarditis. He also emphasized that he had never seen conglomerate or diffuse tuberculous myocarditis in a material representing more than 30,000 postmortem

examinations except when the myocardium was involved in generalized military tuberculosis, and even this not very often. The latter statement is interesting in the light of Wuhrmann's remark that miliary tubercles are commonly encountered in the myocardium in generalized tuberculosis. Šikl further stressed that in generalized miliary tuberculosis the classic subendocardial miliary tubercle of Weigert in the conus of the pulmonary artery may sometimes be encountered. More often the myocardium is involved secondarily to tuberculous pericarditis.

Among the 240 instances of myocarditis there were 3 in which miliary tubercles were observed in the heart. These were part of generalized miliary tuberculosis. In 3 young patients who died from chronic ulcerating pulmonary tuberculosis, the myocardium was the seat of diffuse subacute inflammatory changes, not at all characteristic of a tuberculous infection.

Hodgkin's Disease.—To judge from the literature, involvement of the myocardium in this disease is rare. However, it would perhaps be shown to be more frequent than would be suspected from the literature if in every case of Hodgkin's disease the hearts were submitted to closer scrutiny. Extension of mediastinal masses into the pericardium and myocardium is occasionally seen in routine postmortem material, though such occurrences are not specially reported.

Schlagenhaufer reported 3 cases of Hodgkin's disease of the gastrointestinal tract. One heart was of a yellowish color and presented an irregular speckled appearance. Histologically, the myocardium showed the typical granulation tissue with Dorothy Reed cells. Šikl (1933) mentioned a case in a general review on myocarditis. Dalous, Fabre and Pons reported the case of a 25 year old man with Hodgkin's disease of the mediastinum. The myocardium showed a number of whitish spots which histologically consisted of specific granulation tissue. It is interesting to note that muscle giant cells were also present which were strictly differentiated from the Dorothy Reed type of giant cell. The patient had died suddenly. Without giving any reference, these authors quoted a case of Hodgkin's granuloma in the heart reported by Barre and Desnos. Krueger and Meyer reviewed 60 cases of Hodgkin's disease, including 16 autopsies. The ventricular myocardium was involved twice and the right auricle once. McAlpin in a review of 23 autopsies found nodules in the myocardium recorded in 2 instances. Harrell reported a patient with fulminating Hodgkin's disease. The pericardium and myocardium were involved. He also cited 8 instances from the literature in which the pericardium was involved. Ritvo recently reported an instance of involvement of the pericardium and myocardium.

Boeck's Sarcoid.—Perhaps the few recorded instances in which Boeck's sarcoid involved the heart may be cited here. Bernstein, Kon-

zelmann and Sidlick described epicardial lesions showing the typical granulomatous tissue. They also mentioned that the adjacent muscle was invaded for a distance of 4 to 5 mm. Such epicardial lesions were also noted by Schaumann and Longcope and Pierson. Nickerson mentioned that the myocardium was involved in 1 case. There were a few solitary lesions found in the perivascular fibrous tissue and in the subendocardial regions.

Syphilis.—Syphilitic involvement of the myocardium is still a most controversial subject. Excluding congenital syphilis of the heart, gumma in the myocardium or gummatous myocarditis—by "gumma" is meant a large, grossly recognizable nodular lesion with more or less caseation, and by "gummatous myocarditis," the presence of microscopic gummas—the controversy revolves around the question of whether or not there occurs diffuse myocarditis of a syphilitic nature and a fibrous type, the result of healing of diffuse myocarditis. In 1932 Saphir reviewed the literature pertaining to so-called chronic syphilitic myocarditis and listed the criteria of syphilitic myocarditis recorded in the literature. A critical consideration revealed that morphologically the diagnosis of syphilitic myocarditis could not be made in any of the reviewed cases in the absence of gummas. He summarized the findings in 130 hearts associated with syphilitic aortitis and with insufficiency of the aortic valve. The myocardium in these 130 hearts showed no changes which from a purely morphologic and unbiased point of view could be interpreted as syphilitic myocarditis. All the changes observed might be encountered in other conditions. Spirochetes could not be demonstrated in any of the 130 hearts. Cover slips without tissue, prepared according to the Warthin-Starry method, revealed artefacts that resembled spirochetes. In this study the findings of Warthin, the outstanding proponent of the belief that syphilitic myocarditis not only occurs but, as a matter of fact, is a frequent finding, were analyzed. First, many attempts were made to see whether Warthin's result could be reproduced and his conclusions in this respect confirmed. However, a most diligent and conscientious search proved futile. Later, by using the autopsy material at Michael Reese Hospital and employing first Warthin's technic and later a special technic devised in the laboratory of this hospital (Garvin) Saphir and co-workers sought another explanation of so-called syphilitic myocarditis.

As far as the patient is concerned, it cannot be overstressed that, as Norris so strongly emphasized, "in every syphilitic patient, sooner or later, the heart will be fatally damaged unless . . ." From the point of view of the clinician, it does not make much difference whether the myocardial damage is the result of primary changes at the mouths of the coronary arteries or is due to primary inflammatory changes in the myocardium itself. However, it seems clear from this review and from clinical observations in general that where the blood supply to the heart

is interfered with, particularly if the interference is at the orifices of the coronary arteries, a more serious condition results than from an inflammatory process in various foci within the heart muscle, provided that the inflammation does not involve the conduction system. The saying of the older clinicians that the first failure of a syphilitic heart is usually the last well illustrates this fact.

The main point in question, as in rheumatic fever and tuberculosis, is whether or not it is justifiable to attribute a specific cause to nonspecific histologic lesions. At the present time, with the information on hand, it is my belief that if this is done, much of the firm ground on which pathology is built and which also forms the fundamental principle of clinical medicine will be lost. There are, of course, possible exceptions, as in those instances which can be supported by experimental pathology and medicine. However, in the case of syphilis such experiments at the present time are not apt to throw any light on syphilitic myocarditis. The conception may have to be changed when more information about Spirochaeta pallida becomes available and the various reactions of the host at various times become more clearly understood.

There is no question that Warthin, the master technician as he is sometimes called, found and pictured organisms apparently like spirochetes in syphilitic myocarditis. There is also no question that many a searcher has investigated heart after heart and has not found such organisms. It is known that in congenital syphilis it is comparatively easy to find spirochetes. But it should be pointed out that often such spirochetes are present in the absence of any tissue reaction or inflammatory cells. The question, therefore, is pertinent, as to why not only in the United States but throughout the world reports of the finding of spirochetes which undoubtedly conform with those seen in congenital syphilis and with those seen in primary syphilitic lesions are not encountered with greater frequency. It is well known that it is not easy and that it is a matter of skill and diligent search to demonstrate spirochetes in the aorta and the aortic valve. Šikl and Raška in a case of syphilitic involvement of the aortic valve found within the myocardium large areas of fibrosis in addition to foci of necrosis in part surrounded by leukocytes. By using Kanzler's stain they found spirochetes in the aorta and aortic valve but none in the myocardium.

Norris, reviewing some of the literature and alluding to the controversy on the demonstration of spirochetes, naturally accepted the statements of those who demonstrated spirochetes rather than the denials of those who could not verify the presence of such organisms. If only more investigators were able to find the spirochetes, the whole argument would lose much of its force. Norris stated:

> While willing to agree that I could not find the spirochetes with Warthin's facility, I feel that years of experience had taught Dr. Warthin more about heart

forms of spirochetes than was known by any other living pathologist, and on this fact one is treading on thin ice when one presumably suspects that Warthin saw artefacts and called such artefacts spirochetes. A few practical facts about spirochetes that are not remembered by histologists in general, must also be considered. Spirochetes, in my opinion, do elongate, separate and fragment in syphilitic lesions, and at times they may obscure themselves by their twists, spirals and dissimilar appearances as compared to spirochetes in fetal or acute syphilitic ulcerations. One must admit further that as the syphilis grows older the spirochetes become hidden, quiescent and inactive. Treatment also tends to obscure them.

He also quoted Stokes:

Personally, and from a number of experiences in spirochete staining, and through Warthin's courtesy in allowing me to see a number of his preparations, I believe that we must yield to him as our master in the matter, and ascribe to technical difficulties many of the reported failures to confirm his findings.

The explanations offered by some investigators for the failure to demonstrate spirochetes in supposedly syphilitic myocarditis may be illustrated as follows: Weller and Shaw in a study on trichinosis also referred to the difficulties in the demonstration of spirochetes in the myocardium, even, as they stated, in cases of clearly demonstrable syphilitic myocarditis or when the aortas of the same patients showed countless numbers of easily stained organisms. One must believe, they emphasized, that these observations have a broad biologic significance in that they point to a special evolutionary endowment of the heart muscle with antiparasitic powers not possessed by most of the other tissues of the body.

Hamman and Rich (1934) reported an instance of syphilitic myocarditis. They could not find spirochetes in the heart but demonstrated fine interlacing scars, areas of mononuclear infiltrations, lymphocytes, scattered macrophages, occasional plasma cells and focal areas of necrosis. It seems significant that they remarked that "they fear that it has been the pathologists who have been chiefly responsible for the present reluctance of clinicians to recognize the existence and importance of this disease."

Paullin and Minnich stated that syphilis of the myocardium occurs either as a solitary gumma or as a diffuse subacute inflammatory process involving most commonly the left ventricle. Gumma of the heart muscle is usually located near the base, in the interventricular septum, and has the general characteristics of gumma occurring elsewhere. It is seldom discovered except at autopsy. Subacute myocardial syphilis, described so well by Warthin and others, which perhaps is rarer than other forms of cardiac involvement, usually is seen in the left ventricle. There is diffuse infiltration of the muscular wall by numerous small round cells, plasma cells, fibroblasts, and very occasionally a few leukocytes, completely separating and destroying the heart muscle. These areas are frequently visible to the unaided eye. Another lesion, probably representing a later stage of this subacute process, is found in which most of

the active inflammatory process has disappeared and in its place are large bands of fibrous tissue containing numerous small round cells, healing having occurred with complete destruction of the heart muscle in these areas. Both types of myocardial syphilis are usually accompanied by syphilitic aortitis.

Magill reported 5 cases of unexplained cardiac decompensation. All the patients had syphilis. The myocardium revealed diffuse scarring and round cell infiltrations. It was stressed that these changes suggested a chronic inflammatory process. There was no evidence of chronic infection other than syphilis in any of the cases. There was no sclerosis of the vessels of the kidneys, adrenals or other organs, but the possibility of previous hypertension was suggested. Magill, in discussing syphilitic myocarditis, stated that it seemed rather strange that there exists such marked difference of opinion as regards not only the frequency of syphilitic myocarditis but its occurrence. He may be quoted as follows:

> Most of the objections offered by those who believe that syphilitic myocarditis is infrequent are based on studies of hearts of individuals showing advanced syphilis of the aorta and aortic valve. That such studies may not be inclusive enough is suggested by the autopsied cases of the present study, none of which showed typical syphilis of the aorta. Also, in the 3,000 cases reviewed, there were 11 patients, less than 46 years of age, who came to autopsy showing definite syphilis of the aorta and the aortic valve. In only two of the eleven was there any pronounced infiltration of the myocardium with round cells—all of which would seem to suggest that, if this scarring and round-cell infiltration is syphilitic in origin, the condition may occur quite independently of syphilis of the aorta.
>
> May these cases of unexplained cardiac failure be classified as syphilitic myocarditis? Thus far, the Levaditi and Warthin staining methods have not been successful in demonstrating the *Treponema* in the myocardium. However, much circumstantial evidence is available to support such a diagnosis. In the first place, there is no other plausible explanation; and it is striking that all of the patients gave serological evidence of syphilis. That of itself does not necessarily justify a positive Wassermann being accepted as an explanation for whatever cannot be explained by some other agent. But all five of these cases were in colored males—individuals notorious for their susceptibility to syphilis of the cardio-vascular system. The myocardium of each showed marked infiltration of round cells throughout the scarred areas, between the muscle bundles, and around the smaller blood vessels. Such round-cell infiltration, especially when it is perivascular, is, in other parts of the body, generally accepted as being characteristic of syphilis. Why can it not be due to syphilis when it occurs in the heart muscle?

Magill's reasoning is logical, yet he stressed that the evidence available to support such a diagnosis is circumstantial. And the pertinent question is not why can these changes not be due to syphilis but rather why are they due to syphilis. Again it must be pointed out that it has been shown before and has particularly been demonstrated in this review that the infiltration by round cells, even in a perivascular loca-

tion, and the scarred areas occur in various types of myocarditis and morphologically are not of themselves pathognomonic of syphilis. That myocardial inflammatory changes may occur in syphilitic patients just as in other patients is clear, but the fact that they occur in syphilitic patients does not denote a syphilitic origin for these changes. With respect to this Šikl stated that in a patient showing symptoms of myocarditis and having a positive Wassermann reaction myocarditis may or may not be syphilitic, since they may be mere coincidence of some nonspecific process in the myocardium with venereal infection. Even the apparent effectiveness of antisyphilitic therapy may be misleading.

Reifenstein reported an instance of acute myocarditis simulating acute myocardial infection. He stressed that pathologists have been unable to differentiate the fibrous changes found in the myocardium in known syphilis from the fibrous changes found in other conditions, including arteriosclerosis. This fact and the failure to find spirochetes in the myocardium have been used as evidence against Warthin's concept that a specific form of myocarditis is found in syphilis. Reifenstein felt that it was rather unfortunate that the discussion on syphilis of the myocardium had centered around the question whether or not a specific form of myocarditis other than the gummatous type occurs. This seems pertinent, he continued, because it must be stressed that there is no question that gummas may occur in the myocardium just as in other organs or structures. It is obvious that gummatous myocarditis occurs and has been reported in many instances, but the question arises whether or not there is an acquired syphilitic type of myocarditis, more or less diffuse, showing nothing characteristic of syphilis in the absence of demonstrable spirochetes in the myocardium.

Sohval might be quoted in this respect. He stressed that with omission of the controversial diffuse fibrous type from consideration the disease may be said to assume the form of diffuse interstitial gummatous myocarditis or that of so-called gummatous myocarditis. As a matter of fact, he emphasized that acquired tertiary syphilitic heart disease (exclusive of aortitis with commissural involvement) is uncommon and consists of circumscribed gummatous myocarditis (cardiac gumma) and diffuse gummatous myocarditis. This author also gives a review of the literature on gumma of the heart.

Šikl and Raška carefully examined the hearts of 6 patients who died suddenly from apparent syphilitic aortitis. They failed to find spirochetes in the myocardium. However, in 5 cases spirochetes could be demonstrated in the aorta. They concluded that syphilitic lesions are rare in the myocardium and that it would be hardly possible to explain the genesis of the fibrotic lesions in the heart on a syphilitic basis. On the other hand, they stressed that congenitally the heart may very well be involved in syphilis.

Cabot and Mallory in 1933 (Cabot case 19482) discussed an instance of possible syphilitic myocarditis. There was a considerable increase in fibrous tissue around the blood vessels, and there were numerous areas where occasional muscle fibers were undergoing hyaline degeneration. Infiltrations by lymphocytes and plasma cells and thickening of the intima of coronary branches were seen. Mallory stressed that the changes were perfectly consistent with syphilitic lesions so that he thought he had the right to say that there was progressive myocarditis in this case.

Lami examined the hearts of 30 patients who had been clinically proved to have syphilis. In 8 hearts no important lesions were found; in 12 hearts circumscribed or more diffuse fibrotic lesions were encountered, and in 10 hearts there were lesions described as subacute syphilitic myocarditis. However, he maintained that these lesions were not specific and that therefore the diagnosis may be made only on the simultaneous presence of other signs of syphilis, either clinical or anatomic, on examination of other organs.

Castellano, Cenget and Lascano reported an instance of possible syphilitic myocarditis. Wuhrmann found syphilitic aortitis and myocardial fibrosis in his case 12 and was inclined to believe that the fibrosis was the result of the syphilitic myocarditis. Grieshammer reported a patient with tabes dorsalis. The heart revealed productive interstitial myocarditis with involvement of the pulmonary valve. Histologically there were round cells and plasma cells between the heart muscle fibers and also a few neutrophils and eosinophilic leukocytes. No giant cells were found, and neither spirochetes nor tubercle bacilli could be demonstrated. These changes, the author suggested, might have been the result of an infectious or toxic agent because of the simultaneous finding of severe pyelitis and early pyelonephritis. However, because the patient had tabes dorsalis, the possibility of a syphilitic nature of the myocarditis must also be considered. This case is interesting in that it represents an attempt to diagnose the type of myocarditis from other changes found at autopsy and not from the morphologic appearance of the myocarditis.

Bohnengel presented a patient with syphilitic heart disease and aortic insufficiency, showing cardiac enlargement and congestive heart failure. At autopsy myocarditis was found in the interventricular septum. In two sections searched for spirochetes, none was found. The combined clinical, laboratory and autopsy observations pointed to syphilis as a possible etiologic agent for the production of the lesion and the accompanying disturbance in conduction, but conclusive proof was lacking. He stated that the lesion itself was a nonspecific organic reaction that might have been a response to any one of several types of disease processes, infectious, vascular or toxic, but whether or not it was of syphilitic origin was a question which could not be answered.

In view of the difficulties with which one is confronted in making the diagnosis of syphilitic myocarditis, it is interesting to note that Lisa diagnosed syphilitic myocarditis and acute rheumatic myocarditis, in addition to atresia of the coronary mouths, in the same heart.

Love and Warner are more definite in their statments. They stressed that myocardial lesions in the hearts of 15 patients with syphilitic stenosis of the coronary ostia were similar in nature to those commonly noted as a result of myocardial ischemia.

Nathanson may be quoted as follows:

> As regards the possibility of syphilitic involvement of the myocardium and coronary arteries, I wish to state that the department of pathology at the University of Minnesota Medical School feels decidedly that aside from the occasional gumma of the myocardium the only cardiovascular syphilis is that which affects the aortic orifice and aorta with involvement of ostia of the coronary arteries. I have not been convinced that interstitial changes in the myocardium can be produced by the spirochetes. Certainly many investigators have repeatedly failed to demonstrate the spirochetes in the myocardial lesions. The feeling of the pathology department is that the interstitial changes are secondary to the myocardial ischemia resulting from the coronary orifice involvement and are not inflammatory in origin.

Clawson (1941) examined microscopically five blocks from each of 105 hearts with syphilitic aortitis. A few small fibrotic areas of the type commonly seen in hearts with coronary sclerosis were encountered. Also small proliferative inflammatory areas were noted in a few hearts, and an occasional patch of lymphocytic infiltration was present in a relatively small number, but syphilitic myocarditis was not mentioned. Blocks from 71 hearts were stained by the Levaditi method and examined for spirochetes, but none was found.

Syphilitic myocarditis is described morphologically by Norris (1939) as follows:

> Whenever the muscle is invaded the clinical and pathological features are definite and unmistakable. As a rule, the common lesion is characterized by the occurrence of grey or pale grey white, fairly well defined areas within the left heart wall. These spots usually are not surrounded by zones of hyperemia. They are irregular in size and shape and are fairly firm, containing little necrotic material such as that seen in infarction or tuberculosis, and simulating malignant infiltrations in appearance. Occasionally smaller lesions may be seen in the right heart wall and within the ventricular septum, seldom near the apex or about the auricles or the surface of the heart. Histologically, there is a picturesque reaction composed of infiltrations of lymphocytic cells and fibroblasts with an occasional giant cell and many plasma cells. New, thin walled blood vessels may be quite numerous. The lymphocytes are mostly around the smaller blood vessels. Necessarily, a tissue change in such a heart must react with grave symptomatic features, and the heart loses its normal strength and viability from the disorganization of its structures.

In 1937 Norris reported 3 cases. The myocardial changes in general were described as follows:

> As a rule the muscle is moderately soft and does not have the firm resistant feel and appearance of the hypertensive heart. The auricles are usually thin, roughened and dilated. The epicardium occasionally is covered with thick, pink, edematous adhesions but never has the shaggy, exudative adhesions of the more common types of pericarditis. The typical syphilitic processes in the muscles are most often seen in the wall of the left side of the heart, somewhere near the base, and are recognized as grey yellow or grey white, variably sized, irregular areas, usually not surrounded by hyperemic zones but well defined in type, and which gradually merge into the adjacent tissues. The grey or yellow spots may be quite extensive and numerous, or, on the other hand, only one circumscribed area of involvement may be found. Occasionally there is a diffuse involvement with areas of lighter nature causing the ventricular muscle to have a mottled appearance. The endocardium may be white and definitely thickened. As a rule fibrous tissue streaks may also be seen. The interventricular septum muscle is often involved. Occasionally, as illustrated in this paper, bizarre muscle damage of an aneurysmal nature may occur in syphilitic myocarditis, and large myolitic cavitations with irregular, hemorrhagic, degenerated, yet well defined walls may be present.

He stressed his total agreement with those who state that histologically the typical and constant tissue reaction is one in which lymphocytes, plasma cells and fibroblasts are usually around the vessels and in the connective tissue stroma, adding that in the coronaries most often the picture is one of intimal thickening by endothelial proliferation, hyalinization and scarring by fibroblasts in the media, with considerable collections of islands of lymphocytes in the adventitia. It is emphasized that in all 3 hearts spirochetes were demonstrated by C. V. Weller. Norris' paper gives an illustration of four spirochetes. In comparing these spirochetes with those seen in congenital syphilis it must be frankly stated that they do not look like those seen in the myocardium or liver of an infant with congenital syphilis. However, Norris stressed that these illustrations show various forms of spirochetes (see quoted passage). Yet, if pathologists deviate from the classic conception of the Spirochaeta pallida, and if "broken up" or straightened out spirochetes are taken as evidence of syphilis, such a diagnosis will be made in the future much more often than ever before.

Gumma in the myocardium is very rarely encountered. Šikl (1933) stated that among 18,685 postmortem examinations performed during the period from 1921 to 1931 at the Pathologic Institute of Prague, Czechoslovakia, only 2 instances of gummatous myocarditis were found among 909 cases of acquired syphilis (diagnosis established), including 518 cases of syphilitic aortitis. Clawson (1941) found only 5 instances of gumma in the myocardium in 30,265 autopsies. Relatively more recent reports of gumma in the myocardium are those of Kux, Sohval, von Haam and Ogden, and Braunstein, Bass and Thomas. Cossio,

Vivoli and Caul described a sclerogummatous type of myocarditis. They also included a picture of a spirochete which is not too convincing.

This review on syphilitic myocarditis would not be complete if mention were not made of the so-called "critical" syphilitic myocarditis of Warthin (1925). Recently Corrigan studied this subject and reviewed the pertinent literature. She had observed myocardial infarcts in 5 hearts with syphilitic aortitis. In 2 the infarcts were the result of syphilitic changes in the aorta and at the mouths of the coronary arteries, and in 3 they were caused by concomitant cononary arteriosclerosis and thrombosis. She stressed the histologic similarity between recent infarcts and "malignant syphilitic myocarditis" or acute exacerbations of latent syphilitic myocarditis.

In summary, from the available literature and from a study of this subject over a period of fifteen years it must be concluded that the entity "syphilitic myocarditis," a diffuse syphilitic inflammation with the presence of spirochetes in acquired syphilis, is extremely rare, if it occurs at all. This does not mean that the final word has been spoken, but it should be a stimulus for further exhaustive studies closely linked with the problem of syphilis in general. The heart from every syphilitic patient should be subjected to a careful search for microscopic lesions. Every method available for demonstrating spirochetes should be used. More thorough studies of the cultural characteristics of Spirochaeta pallida and animal experiments are essential, always having in mind the possibility of producing specific myocardial changes, taking into consideration the immunologic state of the host. Perhaps, after a more concerted effort in this respect, more will be known about syphilitic myocarditis.

Blastomycosis.—Kirch pointed out that in instances of generalized blastomycosis the heart may be involved. He stressed that such a condition is extremely rare and also mentioned the older literature. He did not, however, mention LeCount's report and Cleary's studies. The former in 1915 mentioned about 100 miliary nodules in the epicardium in 1 case. Histologic examination showed that only the superficial parts of the myocardium were involved. Cleary in 1904, as quoted by Baker and Brian, on histologic examination found minute blastomycotic tubercles in the myocardium.

Stober studied systemic blastomycosis. He found lesions present in the myocardium in his case 6. However, in the summary he mentioned that myocarditis was found in a few.

Coupal in 1 instance of blastomycosis found that the heart grossly showed several abscesses in the left ventricle and the left auricle. Histologically, the section through the heart muscle showed diffuse infiltration by young fibroblastic cells, indicative of a toxin with specific affinity for heart muscle and acting over a long period. The abscess in

the heart muscle was not surrounded by the usual thick capsule of young connective tissue and contained many polymorphonuclear leukocytes. Its wall was made up chiefly of small mononuclear cells and stratified layers of basophilic giant cells, averaging twelve cells in thickness, and contained enormous quantities of the organisms.

Medlar reported instances of pulmonary blastomycosis, stressing the similarity of this condition to tuberculosis. His first patient showed grossly generalized blastomycosis involving the lungs, kidneys, lumbar vertebrae, joints, bones and skin. The heart on histologic examination showed a small tubercle-like structure composed entirely of mononuclear leukocytes with three yeastlike bodies (looking like Torula).

Baker and Brian studied blastomycosis of the heart in 2 instances. In the first, the patient was a Negro 70 years old. A firm nodule, measuring 2.5 cm. in diameter was present in the right auricle. The surface of the nodule presented smaller elevations and ulcers, the largest of which measured 0.5 cm. in diameter. The cut surface presented yellow and gray areas. There was also adhesive pericarditis. Histologically, just beneath the inner surface of the nodule in the wall of the right auricle were caseous areas containing blastomycetes. A crater had formed and was lined by tissue rich in these yeasts. The nodule showed caseous areas interspersed with connective tissue and granulation tissue. Polymorphonuclear leukocytes were practically absent. Blastomycetes were numerous, inside and outside giant cells of the granulation tissue. The second patient was a Negro 24 years old. The pericardial cavity was obliterated except for several accumulations of pus and caseous material. Gross sections through the heart showed that the epicardial blastomycosis had extended into the myocardium, but there were also small nodules beneath the endocardial surface. Microscopic examination showed large areas of necrosis containing numerous blastomycetes and comparatively few polymorphonuclear neutrophilic leukocytes. Yeasts were also noted within the giant cells.

Martin and Smith in a review of the literature on blastomycosis in general stated that the heart was involved in 9 instances, the lesion having been found in the pericardium, myocardium and endocardium. They believed that it is possible for the cardiac lesions to develop by means of retrograde lymphatic extension. In a study of 13 cases of blastomycosis they mentioned 2 in which there were cardiac lesions. These were cases described and discussed by Baker and Brian.

Torulosis.—Crone, DeGroat and Wahlin reveiwed instances of torula infection. Among the organs mentioned as being involved in torulosis were: the central nervous system, including the meninges, the lungs, the liver, the spleen, the adrenal glands, the kidneys, the testes, the abdominal, thoracic and axillary lymph nodes, the bone marrow and the periosteum. The myocardium as a site of infection was not mentioned.

Actinomycosis.—The rarity of an infection of the heart with actinomyces may be inferred from the report by Sanford and Voelker, who reviewed 670 cases of actinomycosis in the United States. In not a single instance was there cardiac involvement. Kirch also stressed the rarity of this condition. He discussed the pathways of involvement of the myocardium. The infection may reach the heart either as a result of hematogenous metastasis in instances of so-called generalized actinomycosis or may extend to the myocardium from a primary involvement of the neighboring structures. However, he also stressed that primary actinomycosis of the organs of the neck may extend to the mediastinum and thence into the myocardium.

Kasper and Pinner reviewed the literature on this subject, citing 475 instances of actinomycosis, in 5 of which there was a record of myocardial involvement. They reported the case of a 30 year old coal miner who had actinomycotic lesions in the skin of the right arm and thigh. The ventricular wall contained white fibrous tissue in which there were many soft, small foci containing a yellow purulent substance. The purulent inflammation had involved almost the entire thickness of the ventricular walls but there was no rupture into the chambers of the heart. Microscopically, portions of the left ventricle showed the epicardium replaced by granulation tissue. There were scattered collections of lymphocytes and plasma cells. Within the myocardium foci were noted consisting almost entirely of polymorphonuclear leukocytes. Dense connective tissue separated this leukocytic infiltration. The centers of some of these foci contained masses of Actinomyces. It was assumed that the myocardium and pericardium became involved as the result of blood-borne infection. Shapiro found small abscesses in the anterior wall of the left ventricle. Pus-filled polypoid masses projected from between the papillary muscles of the mitral leaflets. Edwards, discussing actinomycosis in children, reported the case of a 10 year old boy with this disease. The myocardium contained numerous minute abscesses, particularly within the right ventricular wall. Edwards stated that the actinomycosis was primary in the bronchioles and extended secondarily into the heart. Šikl (1933), without giving details, also mentioned a few instances of actinomycosis of the myocardium. Uhr, reporting an instance of actinomycotic endocarditis, described scattered small areas of necrosis in the myocardium with infiltrations of small mononuclear cells and polymorphonuclear leukocytes. No ray fungi were found in the myocardium.

Moniliasis.—Polayes reported an instance of subacute endocarditis with systemic moniliasis. The right posterior cusp of the aortic valve was almost completely replaced by a cauliflower-like mass of vegetation composed of monilia, leukocytes and fibrin. This mass projected 4 cm.

upward into the lumen of the aorta. At the base it was continuous with a fluctuating mass of necrotic material and colonies of monilia. This produced a bulging of the right atrial wall, perforating at a point just above the medial leaflet of the tricuspid valve. In addition to these changes obviously present in the myocardium of the right auricle, acute interstitial myocarditis was also encountered.

Sarcosporidiosis.—Lambert reported a sarcosporidial infection in a 32 year old Negress. The heart weighed 360 Gm. The myocardium was of a normal color except in the septal portion of the left ventricle, where there were numerous subendocardial hemorrhages. Sections from the left ventricle showed hypertrophic muscle fibers, some vacuolated and some fragmented. Throughout the myocardium there were a few small areas of fibrosis and about the large vessels there were some lymphocytic infiltrations. Beneath the endocardium were polygonal cells with basophilic cytoplasm, arranged more or less vertical to the surface. In several places they were grouped into submiliary nodules which projected above the surface. Sections from the interventricular septum disclosed a few scattered parasites lying in individual muscle fibers. These fibers were swollen to about twice their natural size and stained more homogeneously than the other fibers in the sections. However, the striations could be seen faintly, and the fibrils were easily distinguishable in the sections stained with phosphotungstic acid and hematoxylin. Situated in the center of each of these fibers was an oval body about which no capusle could be demonstrated. This body was composed of groups of small light blue–staining sickle-shaped or spindle-shaped organisms, measuring approximately 7.0 to 10.0 by 2.0 to 2.5 microns. In the center of each organism was a darker blue–staining nuclear portion that roughly took the same form as the organism. In places the organisms were arranged with their long axes pointing more or less in the same direction, although no trabeculae could be seen dividing the whole body into compartments. Accurate measurements of these bodies could not be made from the sections because of the difficulty in determining their exact outlines, as they did not lie in a single plane. It is stressed that these findings were merely accidental and that there were no symptoms during life which could be referred to this infection.

Hertig reported the case of a 10 day old white girl who had had loose stools since birth and ulceration of the buttocks for two days. There was also purulent omphalitis. At autopsy microscopic foci of necrosis and a moderate number of sarcosporidia, including many early forms, were found in the myocardium. These parasites lay within the myocardial fibers as sharply demarcated oval bodies varying from 7.4 by 11.2 microns to 13 by 45 microns, with the long axis parallel to that of the surrounding fiber. The parasites as seen in individual sections were composed of closely packed oval or spindle-shaped spores,

varying from 6 to 100 in number. No definite wall could be seen in any form possessing less than 13 spores, although beyond that stage a hyaline wall or capsule averaging less than 1 micron in thickness was present. Occasionally, owing to artefact, the cyst wall was pulled away from the surrounding muscle fiber and thus could readily be seen. No septums were seen in any of the forms studied. Slightly over 30 per cent of the parasites in this preparation contained each from 6 to 13 spores, with the higher numbers predominating slightly, although approximately 10 per cent contained each between 50 and 100 spores. The spores averaged 1.8 by 3.7 microns in size. The basophilic nuclear mass was irregular and occupied an eccentric position, often filling one end of the spore. No nuclear membrane could be made out, although the spore membrane was quite definite. Very rarely a suggestion of minute extranuclear basophilic mass could be seen at the end of the spore opposite the nucleus. At no place in the myocardium was there any inflammatory response to the parasites. The remainder of the myocardium was essentially normal except for foci of necrosis associated with a staphylococcic septicemia.

The mode of entrance of the parasite into the body could not be stated with certainty. Hertig also mentioned the cases of Manifold and Lambert as instances of sarcosporidiosis in which the parasites were found in the myocardium.

Toxoplasmosis.—Myocardial lesions in toxoplasmosis should be mentioned. The clinical picture of this disease together with the apparently identical epidemiologic features, as Pinkerton and Henderson stated, justify the assumption that this disease entity closely simulates Rocky Mountain spotted fever and endemic typhus. These authors reported 2 cases. The myocardium in the first showed fusiform accumulations of mononuclear cells between apparently undamaged muscle fibers. A single parasitized cardiac muscle fiber contained a group of eighteen organisms. In the second instance the heart showed microscopically rare necrotic muscle fibers with relatively little cellular reaction. A few myocardial fibers, otherwise normal in appearance, contained large colonies of organisms. These parasitized muscle fibers were so few in number that it was impossible to find them in many of the sections of the myocardium.

Pinkerton and Weinman reported toxoplasma infection in a 22 year old Peruvian man whose death occurred rather rapidly. The heart was dilated but not hypertrophied. A few petechial hemorrhages were noted on the surface of the right auricle. On the surface of the right ventricle were several grayish areas of necrosis, the largest of which measured 8 by 4 mm. On section many similar areas of necrosis, averaging 2 to 3 mm. in diameter, were seen. Several of these were yellowish and had somewhat the appearance of recent infarcts. A few similar

lesions were seen in the left ventricle. Microscopically there were circumscribed foci of coagulation necrosis, with partial or complete disappearance of the outlines of muscle fibers and considerable deposition of fibrin. Thrombi composed of leukocytes and fibrin were numerous in the capillaries and precapillaries, particularly in the peripheral portions of the lesions. A heavy cellular infiltration, predominantly neutrophilic and eosinophilic, was seen in the central portions of these lesions; mononuclear cells were more numerous peripherally. A protozoon answering the description typical of Toxoplasma was present in great numbers, frequently within the cytoplasm of cardiac muscle fibers, and at times in large collections easily seen on examination with the lower power objective. These intracellular collections were frequently seen at the edges of the lesions, where they often occurred in apparently normal muscle fibers, and at a distance from the lesions, in the normal-appearing regions of the myocardium. The parasites were also seen in the central portions of the lesions, singly and in small groups, apparently free. In some instances small capillaries seemed to be occluded with the organisms. Large portions of the myocardium were apparently normal, but there were, in addition to the necrotic foci described, regions in which the picture was that of diffuse myocarditis. In these areas lymphocytes, macrophages and eosinophils were present between the muscle fibers and in the interstitial connective tissue. Not infrequently, focal collections of large mononuclear cells, some of which were multinucleated, were seen around blood vessels, giving a picture somewhat suggestive but not entirely typical of Aschoff bodies. Only rarely were organisms seen in these foci of milder injury.

Cytomycosis.—There are also instances on record of histoplasmosis of Darling (reticuloendothelial cytomycosis) involving the myocardium and apparently causing myocarditis.

In Crumrine and Kessel's case the heart grossly showed over its anterior surface near the base a gelatinous coating with several vague white nodules suggestive of tubercles. However, the authors mentioned that microscopically the heart showed no organism and no material changes.

Dodd and Tompkins, reporting an instance of histoplasmosis of Darling in an infant, stated that the parasites were demonstrated in all of the organs involved and in smears of the cardiac blood. Large mononuclear cells were found in practically all the tissues. The most conspicuous lesions were in the liver, lungs, spleen, lymph nodes and bone marrow.

Humphrey reported the findings at necrosy in 2 such instances. In the first microscopic examination the myocardium showed several large areas in which there were cells packed with organisms, numerous plasma cells and what appeared to be immature lymphocytes. These

areas were often so extensive as to cover a low power field. The organisms (small coccus-like, dark-staining bodies with white halos or capsules about them) were apparently found in endothelial macrophages. In the second instance no organisms were observed in the sections of the heart.

MYOCARDITIS IN VIRUS DISEASE

Typhus.—Wolbach, Todd and Palfrey in an extensive etiologic and pathologic investigation of typhus studied the heart carefully. Grossly the myocardium in 6 cases was pale and of a soft consistency and presented yellowish streaks and points. Microscopically there were slight edema and vacuolation of the muscle fibers and all but a few hearts showed characteristic lesions which made it possible to recognize the processs as those of typhus. These characteristic lesions were nodular areas, most often present in the inner half of the ventricular wall, consisting of collections of cells in which large ameboid and phagocytic mononuclears (endothelial cells) predominated; lymphoid and plasma cells were numerous, and mast cells and eosinophils were fairly common. Polymorphonuclear leukocytes were present in small numbers. They were more numerous when there was necrosis of muscle fibers. The necrosis usually involved only a portion of one or several muscle fibers. It was often impossible to recognize the obliterated blood vessels in these focal lesions. Capillaries filled with endothelial cells and frequently with fibrin thrombi were found in early lesions. A more diffuse infiltration of the myocardium was invariably present in the form of endothelial cells, lymphoid cells and plasma cells, which lay packed between capillaries and (apparently) normal muscle fibers. Kirch maintained that this myocarditis is essentially of the interstitial type. Jaffé remarked that death may be brought about by heart failure. In 20 of 26 hearts he noted inflammatory cells. In 12 there were characteristic nodular infiltrations of inflamamtory cells, mainly lymphocytes, plasma cells and adventitial cells about the vessels. Often the changes were diffuse enough to warrant the diagnosis of diffuse interstitial myocarditis, which may be the direct cause of death.

Pinkerton and Maxcy reported a case of endemic typhus. Microscopically, the heart showed numerous lesions. Many of the precapillaries showed definite intimal proliferation and thrombus formation with perivascular accumulations of macrophages and lymphocytes. The thrombi were chiefly composed of endothelial cells and platelets, but in 1 instance 8 or 10 polymorphonuclear leukocytes were present. A second type of lesion consisted of fusiform collections of cells between spread-apart but not obviously damaged muscle fibers. These cells included macrophages, endothelial cells, lymphocytes, plasma cells, mast cells and polymorphonuclears, their frequency being in the order mentioned. At first glance lesions of this type resembled focal necroses, but

the muscle fibers did not appear damaged. On more careful study it was obvious that the great majority (and, by deduction, probably all) had originated in the minute capillaries of the cardiac wall by a process of endothelial proliferation followed by perivascular accumulation of macrophages and other cells.

Herzog and Rodriguez examined 103 hearts from patients who died of typhus. The left ventricle was dilated, and the heart muscle was flabby. In 97 per cent microscopic changes were found, described as a rule as focal but rarely as diffuse acute interstitial myocarditis. The so-called "myocarditis exanthematica" was characterized by submiliary perivascular nodules, particularly pronounced surrounding precapillaries and capillaries, these nodules consisting principally of adventitial cells, fibroblasts, lymphocytes, polymorphonuclear leukocytes and plasma cells. There was also a proliferation of the endothelial cells lining the capillaries. Often the polymorphonuclear leukocytes predominated. Necrosis was rare. Sometimes the infiltrations beneath the endocardium and within the papillary muscles were more marked. Degenerative changes were rare. Only here and there fatty degeneration was encountered close to the cellular infiltrations.

Rocky Mountain Spotted Fever.—This disease, closely related to typhus, must be considered as a cause of myocarditis. Le Count (1911) stated that the capillaries and small veins of the heart were found practically occluded with leukocytes but that there were no serious consequences from this with the exception of minute hemorrhages beneath the endocardium.

Wolbach, in his classic monograph on this subject, stated that the heart was involved in 2 instances. In the first (case 1) there were small collections of endothelial cells in the endocardium and a few microscopic mural thrombi. In the second (case 5) there were a few minute degenerative lesions of the myocardium, and occasional intravascular and perivascular accumulations of endothelial cells.

Lillie (1931) gave a detailed description of the myocardium. He described areas of transverse fragmentation of muscle fibers and focal areas of fatty degeneration and other degenerative changes, even coagulation necrosis. Vascular endothelial swelling, proliferation to several layers, and necrosis, with or without occlusion by masses of granular oxyphil material, sometimes containing nuclear fragments, were seen in all cases. Such vessels were usually of capillary or precapillary size, and these and some otherwise apparently uninjured vessels were often surrounded by adventitial cellular infiltrations comprising chiefly lymphocytes and, to a less extent, plasma cells, macrophages, mast cells and eosinophils. Similar, often dense, focal cellular infiltrations were seen not obviously associated with vessels. Rickettsias were not identified in the vascular lesions.

Pincoffs and Shaw reported the case of a 55 year old man. The heart grossly revealed several petechial hemorrhages in both the visceral and the parietal pericardium. Microscopically, the muscle fibers seemed rather spread out, and by the use of the Giemsa stain rickettsia-like bodies could be demonstrated within the cytoplasm of the endothelial cells of the subepicardial and interstitial capillaries. Harris reported the case a 5 year old girl who died thirteen days after the onset of the disease. Microscopically, some of the capillaries and smaller arterioles were thrombosed. The surrounding myocardium was infiltrated by polymorphonuclear leukocytes and large mononuclear leukocytes, plasma cells and lesser numbers of lymphocytes. There was a proliferation of lining endothelial cells. Also present was an edema of the myocardium with foci of necrosis invaded by polymorphonuclear leukocytes and mononuclear leukocytes. In other fields the interstitial tissue was infiltrated by plasma cells, mononuclear leukocytes and a few lymphocytes.

Bauersfeld found small foci of hemorrhages in the epicardium and the myocardium and beneath the endocardium. Areas of vascular endothelial swelling, proliferation of fibroblasts and a perivascular lymphocytic and mononuclear infiltration were also seen. These conditions were more prevalent in the right auricle.

Florman and Hafkenschiel reported 6 cases of Rocky Mountain spotted fever of the type occurring in the eastern part of this country. Three of the patients died. The myocarduim revealed swelling and proliferation of the vascular endothelium and perivascular accumulations of mononuclear cells, some of which resembled plasma cells, and others, large lymphocytes and macrophages. Occasionally a thrombus was found attached to the wall of a small vessel, about which were often small foci of necrosis. The muscle bundles in places were so infiltrated with mononuclear cells that the picture resembled that of myocarditis. Rickettsia-like bodies were found in large numbers in the myocardium.

Psittacosis.—In a review of the literature on psittacosis Lillie (1933) mentioned only 1 instance in which the myocardium was involved. This was the case observed by Polayes and Lederer. These authors reported a swelling of the heart muscle fibers and small discrete foci of polymorphonuclear and plasma cell infiltrations in the interstitial tissue.

Wuhrmann reported an instance of myocarditis possibly due to psittacosis (case 14). The heart weighed 290 Gm. There was edema between the heart muscle fibers, and an infiltration of lymphocytes and leukocytes was found in the interstitial tissue. The muscle fibers themselves showed severe degenerative changes and myolysis.

Elizalde and Vivoli studied 9 autopsy cases. Grossly, the myocardium had the appearance of soggy meat. Microscopically, in some instances the pericardium was covered by a thin layer of fibrin with a few leukocytes. There was considerable hyperemia of the myocardium, with

edema separating the muscle fibers. Hydropic degeneration and myolysis were frequently present. There was also slight proliferation of the capillary endothelium.

Yellow Fever.—Myocardial lesions have been rarely reported in yellow fever. Cannell studied the hearts of 29 patients dying from West African yellow fever and the hearts of 9 Macacus rhesus monkeys which had been experimentally infected. Cloudy swelling and granular and fatty degeneration were found constantly in the hearts from the human patients and those from the experimentally infected monkeys. Primary inflammatory changes were not seen in the heart in yellow fever. A secondary response of leukocytes to intense degeneration was observed in 2 human hearts. The distribution of the granular and fatty degeneration was patchy and the intensity variable in both human and M. rhesus hearts. The fatty degeneration was most marked in the neighborhood of the nuclei of the fibers. He concluded that the explanation of the slow pulse in yellow fever was still uncertain, but doubt was thrown on the belief that the slowing was due to the jaundice. However, he expressed the belief that further investigation of the clinical function and the pathologic changes of the bundle of His may lead to a solution of the problem. He emphasized that the lesions in the heart were in themselves not sufficient to justify a diagnosis of yellow fever. The lesions in human hearts and in those of the M. rhesus monkeys were essentially the same.

MYOCARDITIS IN PROTOZOAL DISEASES

The few instances of myocardial changes in protozoal diseases may be mentioned here.

Weil's Disease.—Mollaret and Ferroir reported an instance of fatal myocarditis in Weil's disease. There were swelling of the heart muscle nuclei and chromatolysis. The interstitial tissue was infiltrated by lymphocytes and polymorphonuclear leukocytes. In one region a necrotic focus was demonstrated. They particularly stressed the extreme dilatation of the capillaries. No spirochetes were described in the myocardium.

American Trypanosomiasis.—It may also be pointed out here that Chagas reported involvement of the heart in 2 instances of infection with Trypanosoma cruzi. In the first there was dilatation of both ventricles and of the right auricle. Histologically, the myocardium was infiltrated by macrophages and plasma cells. There was a tendency to invade the epicardium. Most of the inflammatory cells were found in the connective tissue, and there was an infiltration around nerve fibers. Only a slight increase in connective tissue was noted. In the second instance the patient, a 41 year old man, died suddenly. There were dilatation and

slight hypertrophy involving principally both ventricles. Histologically, there was infiltration by mononuclear cells, particularly endothelial leukocytes and plasma cells. Lymphocytes and eosinophilic leukocytes were also encountered. This infiltration was localized to the interstitial tissue. There was extensive fibrosis. It is stated that the lesions were also present in the Keith-Flack node and in the main stem of the bundle of His. Rothschild also commented on the involvement of the myocardium in this disease.

MYOCARDITIS IN HELMINTHIC DISEASES

Trichinosis.—Kirch gave a concise review of the pertinent literature. He stressed the presence of many eosinophilic leukocytes in the inflammatory exudate, though there are cases on record (Gruber) with only a few eosinophilic cells. It was emphasized that the myocarditis is most severe in the fifth and sixth week of the infection. He also discussed the question whether the myocarditis is the result of the presence of the larvae themselves or whether it is caused by poisonous products of the trichinas. The belief is expressed that the trichinas do not settle within the myocardium, though they may temporarily pass through it.

Wehrmann reported the case of a patient who died after an illness of four and a half weeks. Many inflammatory cells were found in the interstitial tissue, often in perivascular locations. These were round cells, occasionally plasma cells and large monocytes. However, the absence of eosinophilic cells was stressed. There was also fatty degeneration of the myocardium. Zoller studied 3 pertinent hearts. The first was from a patient who died in the fifth week of the illness. There was dilatation of the right ventricle. The myocardium showed areas of infiltration by lymphocytes, plasma cells and many eosinophilic cells within the interstitial tissue. There were no trichinas. The second heart also was dilated, and there was hypertrophy of the right ventricle with slight hydropericardium. Microscopically, an increase in connective tissue and foci of scarring were noted. Particularly in the subendocardial layers there were accumulations of lymphocytes and many eosinophilic cells. The patient had succumbed eight weeks after the onset of the disease. In the myocardium of the third heart again large foci of lymphocytes and eosinophilic cells were encountered, but no trichinas. Fatty degeneration was also encountered, and there was a mural thrombus. The patient survived thirty-one days. The author stated that experimentally the myocardium is quickly invaded by trichinas, but that the trichinas disappear quickly and are rarely found after the second week.

Weller and Shaw reported the case of a 40 year old man. The heart showed acute interstitial myocarditis, actually focal, but all parts of

the heart were similarly involved. There were areas of infiltration by lymphocytes and eosinophilic cells. Even though many sections were examined, no trichinas were recognized. They stressed the importance of myocardial lesions in the production of the circulatory failure.

Dunlap and Weller stressed myocarditis in the hearts of patients with trichinosis who died between the fourth and the eighth week of the disease. They emphasized that those who had the opportunity to study such material noted the absence of encysted larvae in the heart muscle even though the skeletal muscles showed at the same time very many encysting and encysted organisms. They mentioned Zenker and Frothingham as the only investigators who had observed the larvae in the human heart. Dunlap and Weller also fed white rats with the larvae digested from trichinous meat. The animals were killed at appropriate intervals, and in every instance the myocardium showed alterative and exudative lesions in all respects comparable to those found in human hearts. Trichina embryos were found in such foci as early as five days after feeding and for some time thereafter. After active migration of the larvae had ceased, the myocardium showed no reaction although encystment of larvae in skeletal muscle was occurring to a marked degree. They concluded that if the myocarditis was toxic in origin it should not have subsided during this stage. As a matter of fact, Graham in 1897 had fed white rats with trichinous meat and found the embryos in the heart muscle eight days later. He remarked that the trichinas are either killed in situ or leave the myocardium by passing back into the circulation.

Pund and Mosteller found larvae in the brain of an 11 year old Negro who showed symptoms of encephalitis. It may be mentioned that three weeks before the onset of the illness he had been vaccinated against smallpox. The myocardium was pale, and microscopically there were scattered, irregular foci of degenerated fibers, and these areas were infiltrated by a few lymphocytes, plasma cells and an occasional polymorphonuclear leukocyte. A few foci revealed slight fibroblastic activity.

Spink recorded 4 cases of trichinous infection with one postmortem examination. The microscopic examination of the heart showed that the interstitial connective tissue and the connective tissue around the small vessels were infiltrated by polymorphonuclear, neutrophilic and eosinophilic leukocytes. No larvae were recognized in several different sections. After sections for microscopic examination had been taken from the heart, it was carefully washed in running water and then digested in artificial gastric juice. The sediment was examined and fourteen larvae of Trichinella spiralis were found. These larvae were of the more mature size of those usually found in skeletal muscle and were not the younger forms found in the circulating blood. This excluded the possibility that they had been present in the blood vessels of the heart.

Summarizing, Spink stressed that the histologic picture of myocarditis occurring in trichinosis is not specific. The process is an active cellular infiltration, usually focal, but distributed throughout the myocardium with the production of necrotic and fragmented fibers. Small hemorrhages may be present in the cardiac tissue in the earlier stages. It is stressed that the cellular response in man is for the most part the lymphocytic series. Occasionally, eosinophils predominate in the inflammatory process. Leukocytes appear to play a slight role, as there are seldom more than a few present. Most of the few patients reported to have had myocarditis died between the fourth and the eighth week of infection. Because of the aforementioned finding of larvae in digested cardiac tissue, Spink stated that the invasion of the myocardium by the parasites appeared to be closely related to the myocarditis. This is in clear contrast to the findings of the majority of the other reports.

Gordon, Cares and Kaufman presented the case of a woman who died from apparent encephalitis. The predominant changes at autopsy were trichinosis of skeletal muscle and toxic "encephalosis." The myocardium was a dull brownish red. Microscopically there were distinct focal infiltrations throughout the myocardium. The majority of cells were histiocytes with numerous mononuclear and occasional neutrophilic leukocytes. The adjacent muscle fibers were disrupted and frequently disintegrated. A number of the cellular foci showed red cell extravasations. No larvae were found. Gruber and Gamper in their discussion of a patient with brain changes, mentioned an associated myocarditis. They believed that the myocarditis was due to the trichinella.

Horlick and Bicknell studied a 52 year old woman who had had the characteristic clinical picture. She died about twenty-nine days after the onset of the illness. At autopsy the heart was soft and brownish. Microscopically there were several areas of necrosis, and the contents of these necrotic areas were missing. There was a marked cellular infiltration around the sides of the missing tissue, many of these cells being eosinophils. An occasional area was seen in which an organism having the characteristics of Trichina could be made out. There was some increase in the fibrous tissue of the heart, and the tissue showed moderate round cell infiltration.

Terry and Work stated that theirs was the tenth patient reported in whom the diagnosis of myocardial involvement was proved accurate by autopsy. This was a 20 year old white woman who died twenty-six days after the onset of her illness. The heart weighed 210 Gm. and was dilated. There were a few small hemorrhages in the subepicardial fat. The myocardium was pale reddish brown, dull and flabby. Microscopic examination showed severe fragmentation of the muscle fibers, with swelling of some and shrinkage of others. The interstitial connective tissue was diffusely sprinkled with inflammatory cells and, as

in the skeletal muscle, numerous collections of eosinophilic and neutrophilic leukocytes, lymphocytes and a few large mononuclear and plasma cells were scattered throughout the myocardium in association with focal necrosis of the muscle fibers. These foci were rarely found in the connective tissue septums and bore no relation to the blood vessels. The centers of a few showed small syncytial masses containing from two to three large vesicular nuclei, and several contained half-coiled embryos.

From this review it may be seen that myocarditis in infections with Trichinella spiralis, though rare, was occasionally encountered. The myocarditis usually occurred between the fourth and the sixth week; at least death resulting from myocardiits occurred at that time. Histologically, it was characterized by involvement of both the parenchyma and the interstitial tissue. Foci of necrosis were frequently seen. Among the inflammatory cells the lymphocytes predominated. Eosinophilic leukocytes were also present. However, though sometimes very numerous, their absence was occasionally stressed, particularly in later stages (Gruber). From experimental studies and some autopsies on human bodies it was clear that larvae were present in the myocardium about a week after the time of infection and then disappeared. However in very few instances larvae in the human heart could still be demonstrated on the twenty-sixth and twenty-ninth days of the infection. Since it seems that myocarditis most commonly leads to death between the fourth and the sixth week and since the larvae are not found in the myocardium at that stage of the disease, the diagnosis of "trichinosis myocarditis" by demonstration of the parasite in the skeletal muscle can be made only rarely.

In regard to echinococcus cysts, Heller (1923) should be quoted as stating that they are not rare in the heart. Mills reported a hydatid cyst in the wall of the right ventricle near the apex. He mentioned a number of case reports of echinococcus cysts of the heart and pericardium. Heller stressed that the parasite selects the loose areolar tissue of the auriculoventricular groove and then may bulge into the adjacent cavities. The cyst or the colony of cysts may cause death by interfering with the action of the heart or by rupturing into one of the adjacent cavities, whence daughter cysts, membrane or detritus is carried into the pulmonary or systemic circulation. He also pointed out that the fact that there have been numbers of cases of hydatid cysts of the heart occurring in subjects with no other involvement suggests that the original embryo, after entering and passing the hepatic and pulmonary circulations, lodges in the heart wall. The development of the cyst, however, is disturbed by the motion of the heart, and therefore early rupture is common.

Von Glahn's unidentified parasite in the heart muscle of a 63 year old patient with an extensively calcified aortic valve and consolidation

of the lung may be mentioned here. The finding was described as peculiar solid bodies lying within the sarcoplasm of the hypertrophied heart muscle. One end of the individual body was bluntly rounded, the other end pointed. Near the bluntly rounded end was an oval vesicular nucleus containing one or more chromatin particles, and close to this nucleus in some instances, a solid round structure. One or more oval vacuoles were present, often near the pointed end. The bodies averaged 52.5 microns in length and 5.5 microns in width. They were usually straight except for slight undulation. Three other somewhat similar bodies were found. The heart muscle containing these bodies was not enlarged. There was no inflammatory reaction about the muscle containing these bodies.

Porter studied a number of patients showing heart changes with hookworm anemia. An autopsy was performed on 1 patient, a 45 year old man, who died suddenly. Ova of Uncinaria americana were found in the feces. The heart weighed 630 Gm. The myocardium was reddish brown and of normal consistency. No evidence of tigering was noted. Microscopically there were areas of edema with widely separated small and larger areas of round cell infiltration. Occasionaly, infiltration by a small number of polymorphonuclear leukocytes and eosinophilic cells was encountered. Foci of fibrosis were seen throughout.

MYOCARDIAL CHANGES IN THYROID DISEASES

There exists an extensive literature on myocardial changes in hyperthyroidism and hypothyroidism. There are also on record experimental studies to show whether or not removal of the thyroid or feeding with desiccated thyroid or thyroxin produces changes in the heart muscle. Because of the extensive literature, it was thought wise to include in this review especially those articles which give some attention to the older literature, those which seem most important from the pathologic point of view and finally principally those which include histologic examinations of the myocardium. Mention is also made of some of the experimental studies on record.

Hyperthyroidism.—Hashimoto in an experimental study described myocardial lesions as a definite entity supposedly characteristic of hyperthyroidism. The lesions consisted chiefly of dense accumulations of large histiocytic cells derived from the clasmatocytes present in the interstitial connective tissue, occurring in small circumscribed areas between muscle fibers or not infrequently in the neighborhood of the blood vessels. These cells may be accompanied by a small or occasionally a rather large number of cells of lymphocytic type. In later stages they may be associated with fibroblasts which, increasing gradually in number, eventually prevail over the other types of cells. The muscle

fibers may be destroyed in confined foci adjoining larger areas of myocarditis. They may show slight but diffuse degenerative changes, apparently occurring independently of the interstitial changes described, such as indistinct cross striations, faint staining with carmine or slight disintegration of the nuclei. The interstitial inflammatory proliferation and the diffuse parenchymatous degeneration may be attributed directly to thyroid intoxication. Hashimoto stressed the fact that the myocardial lesions occurring in experimental hyperthyroidism induced by administration of thyroid correspond to those seen in "goiter hearts," first noted by Fahr (1916). Both consist of chronic nonsuppurative interstitial myocarditis. He concluded that the administration of thyroid can cause not only tachycardia or hypertrophy of the heart but also myocarditic lesions, all of which simulate the functional and anatomic changes found in human "goiter hearts."

Goodpasture described 2 patients the cause of whose death was evidently myocardial exhaustion. The heart of the first was moderately enlarged, and microscopically edema and necrosis were present in patchy distribution. The vessels were normal, and there were no scars or foci of round cell infiltration. The heart of the second patient also showed microscopically edema and foci of necrosis.

Willius, Boothby and Wilson stated that histologically the myocardium of 18 patients showed swollen fibers with indistinct striations and well marked lipoid changes. However, only 5 of the patients whose hearts were examined were under 40 years of age. They believed that it is apparently true that in a person with long-continued pronounced hyperthyroidism the myocardium reveals more advanced fatty changes than are present in the myocardium of a person of the same age without hyperthyroidism. They did not mention myocarditis.

Goodall and Rogers reported the case of a 21 year old woman showing a dilated but otherwise grossly normal heart. Necrosis of muscle fibers was found. There were also foci of cellular infiltration with enormous preponderance of polymorphonuclear leukocytes. The necrosis of the muscles was thought to be evidence of some sort of toxemia and was compared with that seen in diphtheria. They concluded that "it becomes more and more apparent that toxic thyroid secretion produces myocardial degeneration."

W. O. Johnson reported 3 instances of hyperthyroidism with myocarditis. Small areas of perivascular round cell infiltration were found in 2 instances and a hyaline replacement of muscle fibers in the third. He concluded that the changes corresponded closely to myocardial changes in toxic myocarditis, the result of diphtheria or scarlet fever.

Christian (1928) emphasized that with hyperthyroidism there was some evidence of focal degenerative lesions of the myocardium, but in most of the cases myocardial hypertrophy was about all that was found.

There was no interstitial connective tissue increase, no cellular infiltration, no valve lesion and no coronary disease.

W. Lewis from a study of the findings in 12 necropsies on patients with hyperthyroidism concluded that the changes in the heart were characterized by hypertrophy, dilatation and moderate sclerosis of the myocardium, that the cardiac damage might be fairly severe and that the cardiac disorder could not be relieved by treatment. The last opinion was based on clinical rather than pathologic observations. There may also be toxic necrosis in the myocardium caused by toxic thyroid secretion. He suggested that the increased work demanded from the heart results in dilatation, then hypertrophy, and renders the heart more susceptible to secondary noxious influences. Perhaps moderate hypertrophy and dilatation may be present with fatty degeneration and some interstitial myocarditis with fibrosis and lymphocytic infiltration. However, it seemed most likely to the author that there were focal degenerative lesions of the myocardium, though in most of these cases except for hypertrophy the heart muscle was normal. There was no interstitial connective tissue increase and no cellular infiltration.

McEachern and Rake after a review of the literature stated that the available evidence led to the following conclusions: Mechanical factors are rarely responsible for the cardiac phenomena in hyperthyroidism. Cardiac hypertrophy results frequently from hyperthyroidism, both in patients and in experimental animals. Extraordinary contradictions appeared in the reports submitted by different observers concerning the morphologic changes in the hearts of patients dying with hyperthyroidism. The balance of opinion suggested that myocardial scarring, infiltration by round cells and minor degenerative changes were to be found frequently, but no lesions of a specific character had been described.

McEachern and Rake studied the findings in all cases of hyperthyroidism coming to autopsy at the Johns Hopkins Hospital since 1899. There were 27 cases. In 14 instances the hearts were grossly normal. In 8 instances moderate perivascular or intermuscular fibrosis or small foci of round cell infiltration were found. Cardiac hypertrophy was noted in 16 out of 27 hearts. No relationship could be established between the incidence of auricular fibrillation or the duration of hyperthyroidism and the ultimate heart findings.

Rake and McEachern also studied the pathologic changes in the heart and other tissues of animals rendered hyperthyroid with thyrotoxin. The changes in the heart of the hyperthyroid animals were insignificant and varied but little from changes seen in the normal control animals. It was concluded that no significant alteration had been produced by hyperthyroidism. This is interesting when compared with Hashimoto's findings.

Šikl (1933) stated that his own observations had never included inflammatory changes in the heart in exophthalmic goiter. However, he mentioned that Jedlicka examined the hearts in 121 cases of this disease microscopically and found definite inflammatory changes of varying degrees in 6.

Rake and McEachern stated that postmortem and experimental material indicate that hyperthyroidism itself produces no specific lesions in the myocardium. They conceived that the damage produced by physiologic wear and tear, on the one hand, and by any associated infection or disease, on the other, tended to be more accentuated in the patient with hyperthyroidism than in the normal person. The evidence did not suggest the occurrence of a specific toxin producing specific myocardial lesions. It was felt that too much emphasis in the past had been placed on the morphologic changes in the myocardium, with consequent neglect of important alterations in the metabolism and the function of the muscle fibers.

These authors suggested that perhaps the absence of glycogen in the cardiac muscles in hyperthyroidism rendered the myocardium liable to injury, to which it reacts by diminished function, actual structural change and death. However, it may be interesting in this respect to mention that McDonald, Boyle and DeGroat concluded from their work that cardiac failure in hyperthyroidism was not contingent on the presence or absence of glycogen. The function of cardiac glycogen was not primarily to produce energy but, in some manner unknown, to act as a stabilizer between the conservation of energy and its expenditure.

Thomas stated that careful search for pathologic changes in the hearts of patients who died from hyperthyroidism had yielded very inadequate findings. Various reports had been made of noting changes in the heart muscle, and the changes noted reached their high point with Goodpasture's account of 2 cases in which degeneration and necrosis of the heart muscle fibers were observed. The author concluded that hearts of patients dying from thyrotoxic heart failure had a variety of inconstant minor lesions, none of which could surely be ascribed to hyperthyroidism. Some of the changes described are cardiac dilatation and hypertrophy, slight round cell infiltration and hyaline and fatty degeneration of the muscle fibers.

Weller, Wanstrom, Gordon and Bugher found 43 instances of exophthalmic goiter and 90 of adenomatous goiter in a series of 4,200 autopsies. They concluded that their study of 35 cases of exophthalmic goiter showed that with a few exceptions there were no gross or microscopic changes in these cases not equally represented in a carefully matched control series. The exceptions were myocardial fibrosis, endocardial sclerosis and cellular infiltration, the incidence of which was higher in the series with exophthalmic goiter. Focal active myocarditis

for which no etiologic factor could be ascertained other than the hyperthyroid state was observed in only a single heart. The hearts in 55 cases of nodular goiter failed to show any significant difference in the incidence of pathologic changes when compared with a nongoitrous control series.

Menne, Jones and Jones in experimentally produced hyperthyroidism in rabbits found parenchymatous and fatty degeneration of the heart muscles and invasion by histiocytes, early fibrosis and fraying of the muscle fibers. They stated that similar changes may be produced by cardiac overwork, irrespective of the presence of excessive thyroxin in the circulating blood. These studies support the view that the myocardial lesions found in hyperthyroidism are not specific and are probably of mechanical and nutritional origin.

Rössle (1933) described what he called sclerosis of the myocardium in exophthalmic goiter. The sclerosis was supposedly the result of serous myocarditis.

M. P. Schultz studied the induction of carditis by the combined effects of hyperthyroidism and infection. He stated that observers did not agree on the occurrence of extensive morphologic cardiac damage in patients with exophthalmic goiter or in animals given toxic doses of thyroxin. A study of published protocols and case records suggested that such lesions may occur when hyperthyroidism is complicated by infection. Thirty-two rabbits and 13 guinea pigs were given moderate doses of thyroxin or desiccated thyroid while subjected to chronic, focal hemolytic streptococcus infection. In most of them extensive nonpurulent carditis developed similar to that occasionally described in patients with exophthalmic goiter and in animals treated with thyroxin. Such results were obtained only in those infected after hyperthyroidism had been induced, whereas no cardiac lesions developed when thyroxin was given after infection had become well established. This suggests that for the production of such lesions it is necessary that the host experience an alteration in immunologic reactivity during the course of hyperthyroidism. Experiments were described which indicated that immunologic responses were accelerated in hyperthyroidism. The hearts of animals only receiving thyroxin or dried thyroid in the doses used or only subjected to infection did not present such lesions. Likewise, dinitrophenol substituted for thyroxin or desiccated thyroid was ineffective.

From a review of the literature one must conclude that there are no changes occurring consistently in the myocardial tissues of patients dying with hyperthyroidism. Experimental studies also give contradictory results. Among the 240 autopsy records of myocarditis mentioned earlier in this paper there was not a single instance in which the myocarditis could have been attributed to hyperthyroidism. In 1 note-

worthy instance, in which a patient with hyperthyroidism suddenly died after thyroidectomy, acute rheumatic endocarditis and myocarditis were found.

Fahr (1921) and also Fahr and Kuhle discussed myocardial changes in exophthalmic goiter and in status thymicolymphaticus. There were 5 instances of the latter; myocarditis with marked edema between the muscle fibers was noticed in 2; no changes were demonstrable in 3. The changes were thought to be similar to those seen in the hearts of patients with exophthalmic goiter. However, since no evidence of status thymicolymphaticus was seen in 5 patients with exophthalmic goiter and 9 patients with colloid goiter, they do not believe that the myocardial changes in exophthalmic goiter are dependent on coincident status thymicolymphaticus.

Hypothyroidism.—A. Schultz studied a 7 year old child who presented a typical picture of congenital absence of the thyroid gland. The heart showed a peculiar edematous swelling of the aortic valves but otherwise no gross changes. Histologically there was quite a variation in the shape, arrangement and staining quality of the nuclei of the myocardial fibers. The latter showed a varying degree of vacuolation. The interstitial tissue contained apparent edema.

Fishberg (1924) reported the case of a 21 year old patient with hypothyroidism. The heart weighed 350 Gm. The left ventricular wall was thickened, and the myocardium showed small scars. The author stressed, however, that there was marked sclerosis in the aortic arch and in the coronary arteries.

Holzman reviewed the literature relative to cardiac changes in myxedema. He sated that the myxedematous heart is characterized by an enlargement of all four chambers, a slow pulse rate with normal blood pressure and electrocardiographic changes. He did not give any personal postmortem observations.

Means and Lerman reported an instance of atrophy of the thyroid gland. The heart was markedly enlarged, weighing 600 Gm. There was also old endocarditis of the mitral valve with a recent vegetation. The coronary arteries showed much sclerosis and the left circumflex branch thrombosis. Microscopically the heart muscle revealed fibrosis and edema of the interstitial tissue. It seems clear that there were a number of factors in this case which may have led to the myocardial changes.

Ohler and Abramson reviewed the literature on this subject. They quoted those who had expressed a belief in significant myocardial changes and contrasted this opinion with that of observers who held that the changes in the heart were of no great importance. Their own observations were based on a study of 35 patients with myxedema. One of these was examined post mortem, but unfortunately microscopic

studies were not made. The heart weighed 335 Gm., and there was edema of the epicardial fat tissue. The heart muscle grossly was translucent and light red.

Higgins commented on the confusion in the literature concerning the cardiac lesions in myxedema. He stressed that some authors had expressed the belief that the changes were part of the hypothyroid state while others have indicated that they were incidental. The literature was reviewed and the postmortem observations in the hearts cited. He reported 2 cases in which autopsy was carried out. In the first the heart was hypertrophic, weighing 400 Gm. All the coronary arteries were thickened. Grossly, the left ventricular wall showed gradual transformation to fibrous tissue. Attached to the apical part of the cavity was a huge thrombus. Microscopically, at the apex the changes were those commonly found in the fibrous myocardium of coronary sclerosis. The fibrosis was more marked and the muscle more atrophied than usual. The heart of the second patient weighed 450 Gm. The lumens of the coronary arteries were markedly reduced. There was also fibrosis of the myocardium, and a mural thrombus was present. Histologically, the changes were about identical with those of the first instance. The author concluded that it was probable that in the early stages of thyroid deficiency there is a mucin-like infiltration of the muscle fibers which could be overcome by the use of thyroid extract. As the disease progresses, further degenerative changes occur. The heart becomes larger, and coronary sclerosis develops. Because of these early and late changes, degeneration of the muscle fibers takes place, to be followed by extensive fibrosis of the myocardium. He concluded that the condition of the heart in myxedema is a distinct clinical and pathologic entity and should be considered in the differential diagnosis of every obscure cardiac disease.

Higgins also mentioned that at the Massachusetts General Hospital in Boston only 5 autopsy records of changes in the heart in myxedema were available. Four of these records related to interstitial edema with more or less fibrosis of the heart muscle fibers, and one, to fibrosis only.

Gordon expressed the view that the clinical features of "myxedema heart" were due to pericardial effusion in the course of myxedema.

Webster and Cooke studied morphologic changes in experimental myxedema in rabbits. Microscopically, the heart muscles from the myxedematous animals did not take the hematoxylin-eosin stain as well as those from the normal control animals. There was a striking increase in the size of the spaces between the individual fibers. The fibers themselves were swollen, and the number of fibers per square millimeter was decreased. There was increased prominence of the longitudinal striations with partial disappearance of the transverse striations. The nuclei were surrounded by clear spaces and were pyknotic; they

tended to stain deeply. The increase in the perinuclear space was shown clearly in a cross section of the muscle bundle. Frozen sections stained with sudan IV showed that there was little fat in the heart muscle. The clear spaces around the nuclei and between the fibers did not contain fat.

These authors stated that the heart muscles of these myxedematous animals had an average fluid content of 81.9 per cent, compared with 75.6 per cent in the control series. They concluded that myxedema was apparently capable of producing serious myocardial damage in the adult rabbit. It must be noted that they terminated their experiments by killing the animals with carbon monoxide. As will be shown subsequently, carbon monoxide (illuminating gas) produces quite definite changes in the myocardium.

Marzullo and Franco presented the case of a patient with myxedema who died suddenly. The heart grossly and microscopically showed a normal myocardium.

In summary, the divergence of opinion regarding possible myocardial changes in hypothyroidism is obvious from a review of the literature. However, it seems clear that so-called myxedema myocarditis does not exist.

MYOCARDIAL CHANGES IN ACUTE NEPHRITIS, CHRONIC NEPHRITIS AND UREMIA

Supposedly myocarditis occurs occasionally in association with renal disease. In studying the pertinent literature, however, the conviction is gained that reports of such occurrences are often based on clinical evidence alone. Thus primary vascular changes and their effects on the myocardium are not ruled out as the cause of the myocardial failure. The term "nephritis" is sometimes used in the sense of "Bright's disease," and thus includes primary arterial and arteriolar disease. Besides, it must be realized that pericarditis is often encountered as a feature of uremia. Thus, it is easily understood why sometimes the adjacent myocardium may be involved. Such myocarditis, however, is not uremic myocarditis in the strict sense of this term but rather an extension of an inflammatory lesion from the pericardium to the myocardium, whatever the nature of the inflammatory lesion may be. It is extremely difficult, if not impossible, to determine whether or not the primary infection simultaneously caused the acute nephritis and the associated myocarditis.

In this respect it may be pertinent to quote the observation of Lyttle that either no changes are found in the myocardium or, if changes are present, they are more likely the result of other principal diseases. Lyttle stated:

> . . . we have had 6 patients die for whom cardiac failure was the important cause of death—that is, in approximately 150 cases . . . [of acute nephritis].

There were 3 autopsies. One patient had pathologic evidenc ein the heart accounting for the cardiac failure. Two showed no evidence as to what had gone on in the heart to cause failure, nor was there any evidence of vascular damage in other parts of the body. In the patient who had anatomic changes in the heart the slides presented show, in addition to glomerulonephritis, extensive necrotizing arteritis in the kidney and rheumatic endocarditis and myocarditis . . .

Lüscher is supposed to have been the first to describe severe interstitial myocarditis of hemorrhagic character in a nephritic patient. However, he stressed that there was no definite proof of its uremic nature. The myocarditis was histologically identical with isolated myocarditis.

Levy suggested that acute failure of the myocardium may be the first and most prominent symptom of nephritis. Only one autopsy was reported in his series, that of a 49 year old man who had generalized arteriosclerosis and cardiac decompensation. The heart weighed 670 Gm. and showed "chronic myocarditis." Histologic examination disclosed renal arteriosclerosis and acute diffuse glomerulonephritis. From this report it seems more likely that this patient had suffered from coronary sclerosis and consequent myocardial fibrosis in addition to a principally vascular disease of the kidney. The acute nephritis might well have been superimposed on the old lesions of the kidney.

May, Netter and Robert presented autopsy changes in 2 instances of so-called cardionephritis. The term "cardionephritis" was used to signify that cardiac and renal lesions develop in a parallel manner. The histologic picture in the kidney was that of "sclerosing" nephritis with inflammatory foci of the subacute type. The myocardium showed perivascularly and intravascularly distributed polymorphonuclear leukocytes. There were also recent vegetations on the mitral valves. In the second case small red kidneys were observed. The myocardium revealed nodular accumulations of leukocytes, fibroblasts with epithelioid cells and syncytial multinuclear cells. From this report one can neither judge the nature of the renal lesions nor determine whether or not the myocardium in the second case showed specific lesions (Aschoff bodies). There seems to be no relation between the renal and the myocardial changes reported.

Nobécourt stated that in the case of acute nephritis the autopsy discloses a dilated heart. The myocardium may present extensive interstitial myocarditis or interstitial and parenchymatous lesions.

Richter and O'Hare studied the heart in 66 patients with chronic glomerular nephritis, 59 of whom died in uremia. Necropsy reports were available on 59 patients, of whom 53 died in uremia. One third of the 59 hearts showed slight diffuse interstitial fibrosis, usually unrelated to significant sclerosis of the coronary arteries. Moderate patchy fibrosis was seen in 3 hearts with severe coronary sclerosis. The authors

mentioned specifically that when acute fibrinous pericarditis is present the myocardium may present slight degeneration and mononuclear infiltration.

Guthrie studied nephritis in infants and children. Aside from hypertrophy, no pathologic changes were noted in the heart.

Stone (1936) reported 25 cases of acute diffuse hemorrhagic Bright's disease in which autopsy was carried out. He noted in only 1 case necrotization of the afferent arterioles of some of the glomeruli, of the arterioles of the small intestine, right heart muscle and liver, but not of the arterioles of the spleen. This patient was a 15 year old youth, in whom the symptoms of acute renal insufficiency followed acute angina. Death occurred as the end point of uremia. This is definitely an instance of diffuse arteriolonecrosis also affecting the heart muscle, but not an instance of myocarditis.

Master, Jaffe and Dack, attempting to correlate the electrocardiographic changes with the clinical course of acute glomerulonephritis, reported the observations at autopsy in 1 of their patients who died in uremia. The myocardium showed no evidence of acute myocardial disease. Yet they stated that the electrocardiographic changes and the myocardial insufficiency bespoke acute myocardial changes. It was therefore surprising to them that the hearts of 6 additional patients showed no gross or microscopic changes. In 1 heart there were numerous small foci of lymphocytes. They concluded that capillary derangement, toxic or chemical in nature, was the principal change in the heart in such cases.

Aldrich reported 6 autopsies on children who died from acute postinfectious hemorrhagic nephritis. He stressed that myocarditis did not appear prominently among the lesions in these patients. He also referred to 12 autopsies on children with chronic nonspecific nephritis. In 3 of these children cardiac changes were noted clinically. No reference was made to myocardial lesions noted at postmortem examination.

Feller and Hurevitz reported the cases of 2 patients with acute diffuse glomerulonephritis, clinically diagnosed. Autopsy was performed in 1 instance. There were acute glomerulonephritis and general arteriolitis, the latter involving also the arterioles of the heart muscle. In the second patient biopsy demonstrated arteriolitis in the deltoid muscle. The conclusion was reached that acute nephritis is part of a widespread vascular disease which occasionally is severe enough to be called panarteritis. Many patients who seem to have acute nephritis with cardiac failure actually have panarteriolitis with involvement of the myocardium. This seems pertinent. In other words, the authors' patient at autopsy probably did not have primary glomerulonephritis, but in reality primary arteriolonecrosis and arteriolitis. It has been known

for some time that such changes in the vessels are not confined to the kidney but often occur generally. The resulting myocardial changes, however, should not be confused with myocarditis.

Fishberg (1939) stressed that in the febrile patient with acute glomerulonephritis the myocardium may be injured by the toxemia, although microscopic examination rarely reveals much change.

Clark found in the wall of the left ventricle numerous irregular white areas measuring 2 or 3 mm. in diameter. There was no microscopic description. The patient was a 13 year old girl whose kidneys revealed severe occlusive arteriolosclerosis and foci of hemorrhage and necrosis in the parenchyma. This condition apparently does not fall in the nephritis group. More likely it should be considered as arteriolosclerosis, perhaps arteriolonecrosis. The whitish areas in the myocardium were probably scars.

Gouley carefully studied the histologic changes in the myocardium in uremia. Because of the absence of inflammatory changes he suggested the term "uremic myocardiopathy." He described vacuolation due to fatty degeneration or swelling of myocardial fibers. However, close inspection indicated that this fatty degeneration differed from other types of such degeneration. There was a tendency toward subepicardial rather than subendocardial localization as seen in "tabby cat" or tigroid fatty degeneration. The fatty vacuolation in uremic myocardial degeneration usually was very fine. It may be so fine as to escape notice in routine examination, or there may be difficulty in differentiating it from hydropic vacuolation. In advanced degenerations larger droplets of fat were also numerous, but seldom was the vacuolation as marked as in pernicious anemia or in the degeneration occurring with some infections. In some instances the vacuolation gave a very fine moth-eaten appearance to each fiber. Hyaline degeneration and a tendency toward marked swelling of the muscle fibers were seen. The latter were often so increased in size as to diminish greatly the interstitial space in many areas. This swelling exceeded any enlargment due primarily to cardiac hypertrophy. The outline of the muscle fibers appeared quite indistinct. Also a homogeneity suggestive of hyalinization could be made out. There was usually little or no cellular infiltration. In some cases scattered monocytes and an occasional neutrophilic or eosinophilic leukocyte were noted. Only in 2 instances, in this series of 34, could what might be termed a moderate degree of cellular infiltration be recognized. In conformity with the standard nomenclature, the term "uremic myocarditis" would therefore not be truly acceptable.

Herrick and Tillman studied the changes at necropsy in 11 cases of toxemias in pregnancy. In 4 cases there was chronic glomerulonephritis and in 7 a primary cardiovascular disease with arteriosclerosis. The

hearts were hypertrophic and showed fibrosis and varying degrees of vacuolation, but there was no evidence of myocarditis.

Hearts have been studied in instances of so-called tubular nephritis (nephrosis). Wolbach and Blackfan noted in 2 of 8 such instances only moderate interstitial edema.

Calcific fibroblastic changes in the myocardium in chronic glomerulonephritis with or without severe changes in the parathyroid glands were described recently by Aldrich, Bolman, Brown and Ginsburg, and Gouley.

It may be of interest to mention briefly an experimental study on nephritis. Smadel and Farr studied rats in which nephritis was produced by the administration of an antikidney or nephrotoxic serum. A certain number exhibited chronic progressive nephritis without renal failure. Autopsy revealed in these principally the presence of a fat or of calcium in the media and reduplication of the internal elastic membrane of coronary arteries and "fibrous myocarditis," or myocardial scarring. In a certain number renal failure was present, and these rats died with chronic renal insufficiency. Autopsy revealed in these acute focal necrosis of cardiac muscle fibers (visible grossly as yellow flecks beneath the epicardium and the endocardium). In the majority of cases the cellular reaction in and about such areas of degenerated muscle fibers was mononuclear; in an occasional case it consisted of polymorphonuclear leukocytes and in rare instances it was absent. In certain areas cellular collections surrounded muscle fibers which retained their striations. Large mononuclear cells and an occasional multinucleated cell were seen here. Five animals of this group had in addition old scarring of the myocardium, and 4 showed fibrinoid swelling of the ground substance in their acute lesions.

From this review it seems clear that myocarditis does not occur as a result of acute or chronic nephritis, or uremia, per se. Degenerative changes may be found in the heart muscle as in any wasting or chronic infectious disease. Vascular changes similar to those seen in the kidney in arteriolosclerosis or arteriolonecrosis (nephrosclerosis of either variety) may also occur in the myocardium. Uremic pericarditis may extend into the myocardium. Whatever may have caused the acute nephritis may also cause the myocarditis.

Among the 240 instances of myocarditis mentioned earlier in this paper there were included 3 in which acute nephritis was also present and 2 in which myocarditis was combined with chronic glomerulonephritis. In the former 3 instances the myocarditis was acute and apparently caused by the same infection that caused the nephritis. In the 2 cases in which there was associated chronic glomerulonephritis, the myocarditis was of a more subacute nature, and the definite cause could not be determined at autopsy.

MYOCARDIAL CHANGES IN VITAMIN DEFICIENCIES

Most of the few available articles concern beriberi. Because the majority of the investigators agree that in these instances true myocarditis does not occur the subject does not actually fall within the scope of this review, and I shall mention the contributions to it only cursorily.

Mebius believed that a hydropic degeneration of the heart muscle fibers is the primary change in beriberi. The right ventricle and conus pulmonale are particularly involved. There is also some edema present, with only a few leukocytes in perivascular locations. Keefer noted dilatation of the right ventricle of the heart with fatty infiltration and moderate degeneration of the muscle fibers.

Wenckebach (1932) also stressed the dilatation of the right ventricle, particularly pronounced in the region of the conus pulmonale. The right auricle was likewise greatly dilated, and there was interstitial edema of the myocardium. In 1934 he stressed sarcolysis of the muscle fibers. This is described as giving the appearance of swelling and liquefaction to the whole content of the muscle fibers. In spite of the swelling of the sarcoplasma, the striation still may be present. The interstitial edema may perhaps be identical with that described by Eppinger and others as "serous inflammation" (see a subsequent section under this heading). However, the absence of any vestige of inflammation is stressed. This seems an interesting observation particularly because, as stated elsewhere, end stages of "serous inflammation" may be recognized by a new formation of fine strands of connective tissue throughout the myocardium. Thus such scars in the absence of known causative elements may perhaps indicate an old serous inflammation.

Weiss and Wilkins (1937 *b*) remarked that of the vitamin deficiencies lack of vitamin B_1 is the most important cause of cardiac disturbances, stating that the myocardial disturbances reported in rickets and scurvy may be caused by a simultaneous deficiency of vitamin B. The myocardium shows hydropic degeneration of the muscle fibers involving also those in the conduction system. There is an increase of the intercellular substance but an unaltered water content. Intercellular edema is noted. The same authors (1937 *a*) found that 9 of 30 patients showed an increase in heart weight and a considerable degree of dilation of cardiac chambers, particularly of the right ventricle. Histologically there were hydropic degeneration of myocardial fibers, swelling of collagen, perivascular edema and separation of myocardial bundles. Stress was placed on the observation that the histologic changes were not regular, specific or even characteristic of beriberi.

In regard to pellagra these authors stated that when it occurs in its pure form the heart at postmortem examination is small or normal, owing to the frequent presence of dehydration and emaciation. Histo-

logic changes, if they have occurred, are only those seen in brown atrophy. As far as vitamin D deficiency (rickets) is concerned, right ventricular and left ventricular hypertrophy of the heart have been reported. The microscopic changes are not unlike those seen in beriberi. They expressed the belief that in such instances one is justified in assuming that there is concomitant vitamin B deficiency and that the pathologic changes are due to that.

The experiments of Thomas, Mylon and Winternitz are of interest in this connection. In rats and hogs fed a diet deficient in potassium and vitamin B severe myocardial lesions developed, characterized by necrosis of muscle fibers and marked cellular infiltration (chiefly mononuclear). An adequate intake of potassium or vitamin B was sufficient to prevent damage to the heart. Deficiencies in B_6 and potassium led to cardiac injury in rats, while deficiencies in either thiamine or riboflavin and potassium produced no significant changes.

In regard to scurvy, Erdheim's observations must be mentioned. As early as 1918 he reported that scurvy in children (Barlow's disease) may be associated with cardiac lesions. Two thirds of the hearts of children who had died of scurvy showed hypertrophy of the right ventricle. In more severe scurvy both ventricles were hypertrophied. No clinical or histologic studies were made.

Bessey, Menten and King reported extensive fatty changes in the myocardium in pigs with scurvy.

Wolbach (1937) stated that degeneration of cardiac muscle was noted in vitamin C deficiency in human beings and experimentally in guinea pigs.

Taylor in an experimental study stated that scurvy produces cardiac lesions in the guinea pig. The pathologic changes are those of nonspecific valvulitis, myocarditis and occasionally pericarditis. The lesions often contain gram-positive organisms even though no organisms were injected. In the acute lesions, polymorphonuclear leukocytes predominate; in the chronic lesions, endothelial cells, lymphocytes and fibroblasts predominate.

McBroom, Sunderland, Mote and Jones studied the effect of acute scurvy on the guinea pig heart. They stated that acute scurvy produces degenerative changes in the cardiac valves and in the myocardium as well as definite proliferative lesions along the line of closure of the valves. These lesions are equally prevalent and severe in total scurvy whether or not there is superimposed infection. The experimental studies made by Rinehart and Mettier on scurvy with superimposed infection and the production of myocardial changes have been mentioned before.

Though not directly related to vitamin deficiency, it may be mentioned here that Tannenberg observed hydropic degeneration of the

heart muscle fibers as a result of experimental treatment of rabbits with insulin. Also noted were the presence of scavenger cells and a slight round cell infiltration in the interstitial spaces of the myocardium.

MYOCARDITIS IN POISONING

Alcoholism.—References are also found in the literature to myocardial changes resulting from alcohol poisoning. Practically all these references are clinical reports such as the one by Hanns and Warter. However, Langeron spoke of alcoholic myocarditis. He described a dissociation of muscle fibers and perivascular areas of fibrosis. Occasionally, minute infarcts were present in the myocardium, supposedly the result of prolonged dilatation of the vascular bed. Secondary to the infarcts, inflammatory changes were encountered locally. White (1931) stated that alcohol in strong concentrations can, without doubt, injure the myocardium. In 1937, however, he was more cautious, stating that alcohol in strong concentrations can perhaps injure the myocardium. It may also be pointed out that in a number of the cases of myocarditis reported by Wuhrmann indulgence in alcoholic beverages was stressed in the history. Wuhrmann seemed inclined to attribute to alcohol at least some etiologic moment.

Poisoning by Illuminating Gas.—Myocarditis may be due to illuminating gas. According to Kirch, Zondek was apparently the first to describe the cardiovascular system in instances of poisoning by illuminating gas. Kirch also quoted Liebman and other earlier workers. The lesions in the myocardium were characterized by hemorrhagic necrosis, the periphery of which showed inflammatory changes, particularly the presence of polymorphonuclear leukocytes. It was stressed that the papillary muscles in the left ventricle are particularly prone to show these changes. Walcher reported 5 instances of carbon monoxide poisoning. The principal changes were hemorrhages in the pericardium and the myocardium, particularly in the papillary muscles. Microscopically, waxy degeneration, hemorrhages and an infiltration by polymorphonuclear leukocytes were noted. He also mentioned the frequent finding of fragmentation of the muscle fibers. He suggested that the changes are in some respects similar to those seen in diphtheria and implied that the degenerative changes, hemorrhages and necrosis occur primarily, while the inflammatory changes are simply secondary manifestations. Pozhariskiy described the findings in a patient dying from illuminating gas poisoning. Grossly, hemorrhagic spots were observed in the myocardium. Microscopically there were fragmentation, fatty degeneration, focal necrosis and actual myomalacia. He suggested three principal causes for the myocardial changes: the direct effect of carbon monoxide on the tissues; the possible effect of anoxemia

or occasionally of actual thrombosis of smaller blood vessels and, most likely, atonia of the vascular system with resulting stasis and subsequent necrosis.

SEROUS MYOCARDITIS

Eppinger, Kaunitz and Popper defined serous inflammation as the condition in the tissues brought about by the presence of plasma outside the capillary wall. They admitted that this definition is not exactly correct since the presence of plasma within the tissues is more likely part of a symptom complex of a generalized disease than a clearly defined localized process. Such serous inflammation may involve the myocardium. Thus these authors referred to serous myocarditis in instances of serum disease, burns, beriberi, exophthalmic goiter, pregnancy, infectious diseases, malignant nephrosclerosis and others. The significance in the concept of serous myocarditis lies in the fact that, as the authors stated, the plasma outside the capillary walls may stimulate a connective tissue overgrowth. As Schürmann and MacMahon stated, the plasma outside the vessel wall injures the tissues (*Dysorie*) and thus also an explanation is given for the new formation of thin, lacelike connective tissue. As mentioned before, Lindberg suggested that perhaps isolated myocarditis is an end stage of serous myocarditis. Rössle (1934) also mentioned serous myocarditis and attributed sclerosis of the myocardium to serous myocarditis in an instance of Barlow's disease (scurvy). Perhaps myocardial fibrosis not accompanied by coronary disease, sometimes encountered in routine postmortem examinations, may be explained in this fashion. Though it is tempting to ascribe such serous inflammation as the cause of some myocardial changes, it must be expected, if the conception of Eppinger and co-workers is correct, to find similar changes not only in the myocardium but, in every instance, also in other organs and structures. In some of the author's observations this was found. However, more recorded cases with examination of all organs are essential before the role of "serous myocarditis" can be correctly evaluated.

SUMMARY

The incidence of myocarditis and its clinical significance are subject to dispute. There are those who believe that myocarditis occurs frequently and that clinically it is not particularly serious; there are others who think it is rare and of great clinical importance. Little correlation exists between the clinical signs and symptoms and the demonstrable inflammatory lesions of the heart muscle. While the pathologist is inclined to ascribe the sudden death of a patient to myocarditis, the clinician, because of the absence of recognizable clinical evidence of

damage of the heart muscle, is often reluctant to accept myocarditis as the cause of death. However, abrupt death is frequently reported in instances of myocarditis.

In an analysis of autopsy material comprising 5,626 cases, myocarditis was encountered in 240 cases (4.26 per cent). This material was taken from a general hospital, and no cases of contagious diseases were included. The following instances of myocarditis were noted: myocarditis in association with subacute bacterial endocarditis, 44; myocarditis in the form of abscesses in association with pyemia, 32, and in the form of an acute diffuse change, 12; rheumatic myocarditis with the presence of outspoken Aschoff bodies, 30; acute and subacute myocarditis without the presence of definite Aschoff bodies in association with acute endocarditis of the rheumatic type, 24; acute myocarditis associated with bronchopneumonia, 19, and with lobar pneumonia, 7; isolated (Fiedler's) myocarditis, 15; myocarditis in association with acute bacterial endocarditis, 14; myocarditis in chronic diseases such as chronic duodenal ulcers, ulcerative colitis and carcinoma, 12; myocarditis in the presence of bronchiectasis, 8; myocarditis in the presence of meningococcic meningitis, 2, and in the presence of streptococcic and of pneumococcic meningitis, 4; myocarditis in tuberculosis, 6 (in 3 of the instances miliary tubercles were seen and in 3 diffuse myocarditis); myocarditis in association with pyelitis, 4; myocarditis in the presence of acute glomerulonephritis, 3, and in that of chronic glomerulonephritis, 2; myocarditis in congenital cardiac anomalies, 1; myocarditis in postdiphtheritic disease, 1.

The more recent literature on myocarditis occurring as a disease entity or a sequela in infectious diseases is reviewed. Reports of fetal myocarditis are extremely rare. Myocarditis in contagious and infectious diseases, not necessarily associated with endocardial lesions, is discussed. Primary degenerative changes and secondary inflammation are found particularly in diphtheria, typhoid fever and influenza (grip, "flu" and like conditions). Myocardial changes in scarlet fever are characterized by an involvement of the interstitial tissue, though the heart muscle fibers may also be replaced by inflamamtory cells. Myocarditis occurring in instances of infection of the respiratory tract is discussed, myocarditis as occurring in pneumonia being stressed. Meager reference is also made to myocardial changes in measles, mumps, whooping cough, variola, varicella, paratyphoid and dysentery.

Meningococcic myocarditis is characterized by a hemorrhagic exudate with the early appearance of endothelial leukocytes, destruction of muscle fibers and presence of intracellular gram-negative diplococci. Gonococcic myocarditis is often found in association with gonococcic endocarditis. Abscesses of various sizes may be present in the myocardium. Isolated involvement of the myocardium occurs in gonococcic

infection. Myocardial changes are described in tularemia; the lesions are principally foci of necrosis with lymphocytic infiltrations.

The literature on isolated myocarditis is relatively extensive. Apparently the term "isolated myocarditis" denotes inflammatory changes in the myocardium of wide variety and of varied etiologic background having in common an isolated and nonspecific involvement of the myocardium in the absence of inflammatory changes in the endocardium or pericardium and of unknown cause. Instances of isolated myocarditis may be divided into two groups, those in which there are more or less diffuse inflammatory lesions in the myocardium and those in which granulomatous lesions are present. Various etiologic agents have been held responsible for these granulomas, and often syphilis or tuberculosis has been suspected but not proved to be the underlying condition. More recently a special form of hypersensitivity, particularly that due to arsphenamine, has been held responsible for this form of myocarditis. As long as the cause is not known the term "granulomatous" seems adequate. The diffuse form of isolated myocarditis is not characteristic histologically.

Myocardial lesions in association with subacute bacterial endocarditis are common. They consist of abscesses, diffuse acute inflammatory changes, particularly pronounced in the interstitial tissue and consisting mostly of infiltrations of polymorphonuclear leukocytes and lymphocytes, foci of perivascular infiltrations and occasionally Aschoff bodies. Often minute organizing infarcts are encountered. Inflammatory changes are often present in the myocardium in instances of acute bacterial endocarditis. Foci of acute inflammatory changes, particularly pronounced in the interstitial tissue, are significant.

Though reports of abscesses of the myocardium are unusual, this study shows that they are common in instances of pyemia. Clinically, they are regarded as occurring terminally. The clinical symptoms of myocarditis and the type of death of the patient probably depend on the number and the localization of the abscess.

Though the explanation of rheumatic fever as a form of allergy is attractive, it is at best a hypothesis founded on animal experiments. If rheumatic fever is to be considered an allergic phenomenon, the Aschoff body must be discarded as the specific histologic stigma of rheumatic myocarditis. Thus the significance of the Aschoff body has aroused much discussion in recent years. However, from a critical review of the literature and from studies of many hearts it appears clear that rheumatic myocarditis is a specific disease entity, probably caused by a specific though unknown, agent, the Aschoff body being the characteristic granuloma. Structures which do not conform to the classic description should not be definitely classed as Aschoff bodies though they may resemble them. Aschoff bodies so far have not been produced experi-

mentally. There seems to be not a single instance on record of Aschoff bodies in association with Sydenham's chorea in the absence of rheumatic fever.

Myocardial changes occurring in the Libman-Sacks syndrome are also discussed briefly.

In regard to tuberculous myocarditis three main types are differentiated, namely, the nodular, the miliary and the diffusely infiltrative. The last should be accepted only if the histologic changes are undoubtedly characteristic of tuberculosis or if the presence of the tubercle bacillus can be demonstrated either by guinea pig inoculation or by staining methods. Involvement of the myocardium in Hodgkin's disease, to judge from the literature, is apparently rare. Extensions of mediastinal masses into the pericardium and the myocardium are occasionally seen in routine postmortem material, though such occurrences are not especially reported. Rarely may the myocardium be involved in Boeck's sarcoid.

From the available literature and from a study of this subject over a period of fifteen years it must be concluded that in acquired syphilis the entity syphilitic myocarditis, characterized by diffuse syphilitic inflammation and the presence of spirochetes, is extremely rare if it occurs at all. In congenital syphilis, however, myocardial lesions with the presence of spirochetes are occasionally encountered. Gummas are rarely seen. In a very recent report it was stated that gumma in the myocardium was encountered in only 5 of 30,265 autopsies.

The myocardium may be involved in blastomycosis, actinomycosis, moniliasis and sarcosporidiosis. The respective parasites are occasionally encountered in the myocardium. Likewise, myocardial lesions are reported in toxoplasmosis and histoplasmosis.

Typhus myocarditis is not rare. According to a recent report, 97 per cent of patients who died of typhus showed inflammatory lesions in the myocardium. Such lesions are usually focal, rarely diffuse. Myocarditis is also seen in Rocky Mountain spotted fever; occasionally rickettsia-like bodies are found in large numbers in the myocardium. Rarely does yellow fever produce myocarditis.

Among helminthic diseases, trichinal disease is the one with which myocarditis is most frequently associated. The myocardial lesion usually occurs between the fourth and the sixth week following infection; at least death from myocarditis occurs at that time. Histologically, the lesion is characterized by an involvement of both the parenchyma and the interstitial tissue and by foci of necrosis. Among the inflammatory cells the lymphocytes predominate, but often many eosinophilic leukocytes are also present, though their occasional absence is stressed. From experimental studies and some autopsies on human subjects it is clear that larvae are present in the myocardium about a week from the time

of infection and that they then disappear. It is therefore evident that the diagnosis of trichinal myocarditis is not necessarily dependent on the finding of larvae in the myocardium. Mention is also made of the involvement of the myocardium in echinococcus disease.

From a review of the literature one must conclude that there are no consistent myocardial changes described in patients dying with hyperthyroidism and hyopthyroidism. So-called myxedema myocarditis does not occur. Myocarditis caused by acute or chronic nephritis per se or by uremia is a myth. Degenerative changes may be found in the heart muscle in such diseases, as in any wasting or chronic infectious disease. Such vascular changes as are seen in the kidney in arteriolosclerosis or arteriolonecrosis (nephrosclerosis of either variety) may also occur in the myocardium. Uremic pericarditis may extend into the myocardium. Whatever may have caused acute nephritis may also have caused myocarditis.

Myocardial changes are described in vitamin deficiencies. Most of the available references concern beriberi. The principal changes in the myocardium are of a degenerative nature, but there also occurs a type of inflammation described as "serous inflammation." This is thought to be a reaction of the tissues to the presence of plasma outside the capillary wall. The plasma apparently injures the tissues, with the result that there is gradual new formation of a thin, lacelike connective tissue.

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Notes and News

Awards.—The Copley Medal has been awarded by the Royal Society to Sir Thomas Lewis for experimental researches in clinic and laboratory on the heart and circulation and their disorders.

The Bailey K. Ashford Award of $1,000 and a bronze medal of the American Society of Tropical Medicine have been presented to Lloyd E. Rozeboom, of the Johns Hopkins University, formerly medical entomologist of the Gorgas Memorial Laboratory at Ancon, the Canal Zone, in recognition of his work in tracing malaria transmission to a variety of mosquitoes suspected, but never demonstrated, to be carriers of the disease.

The Mead Johnson Awards have been presented by the American Academy of Pediatrics to René J. Dubos of the Rockefeller Institute for Medical Research and to Albert B. Sabin, associate professor of pediatrics in the University of Cincinnati. The first award was given to Dr. Dubos for his discovery of gramacidin, a bactericidal agent of vegetable origin, and the second award was given to Dr. Sabin for his work on virus diseases of the nervous system.

Edward H. Hatton, who recently retired as professor of pathology and bacteriology at Northwestern University Dental School, has received the Callahan Award of the Ohio State Dental Society for 1941. He will continue to serve as general secretary of the International Association for Dental Research, with an office at Northwestern University.

The Lister Medal for 1942, which is given in recognition of distinguished contributions to surgical science, has been awarded to Evarts A. Graham, professor of surgery in Washington University, and he will deliver the Lister Memorial Lectures in 1942, or later, under the auspices of the Royal College of Surgeons of England.

Society News.—The American Association for Cancer Research will meet in Boston on March 30 and 31. Members desiring to present papers should so inform the secretary, A. A. Thibaudeau, 143 High Street, Buffalo, at the earliest possible moment before Feb. 1, 1942. Every request for place on the program must be accompanied by a brief abstract of the paper to be presented.

In March 1942 the Federation of American Societies for Experimental Biology will issue the first number of a quarterly publication to be named the *Federation Proceedings*. The editorial board will represent the five constituent societies of the federation, which includes the American Society for Experimental Pathology. The managing editor will be D. R. Hooker, 19 W. Chase Street, Baltimore.

University News, Appointments, etc.—Mataro Nagayo, outstanding Japanese pathologist and president of the Japanese Foundation for Cancer Research, has died at the age of 63 years.

William V. Knoll has been appointed Littauer fellow in pathology at the Huntington Hospital, Boston.

Willard C. Rappleye, commissioner of hospitals of the city of New York, and dean and professor of medical economics, Columbia University College of Physicians and Surgeons, has been elected president of the Josiah Macy Jr. Foundation, New York, effective January 1, to succeed the late Ludwig W. Kast.

Obituaries

FRANK BURR MALLORY, M.D.
1862—1941

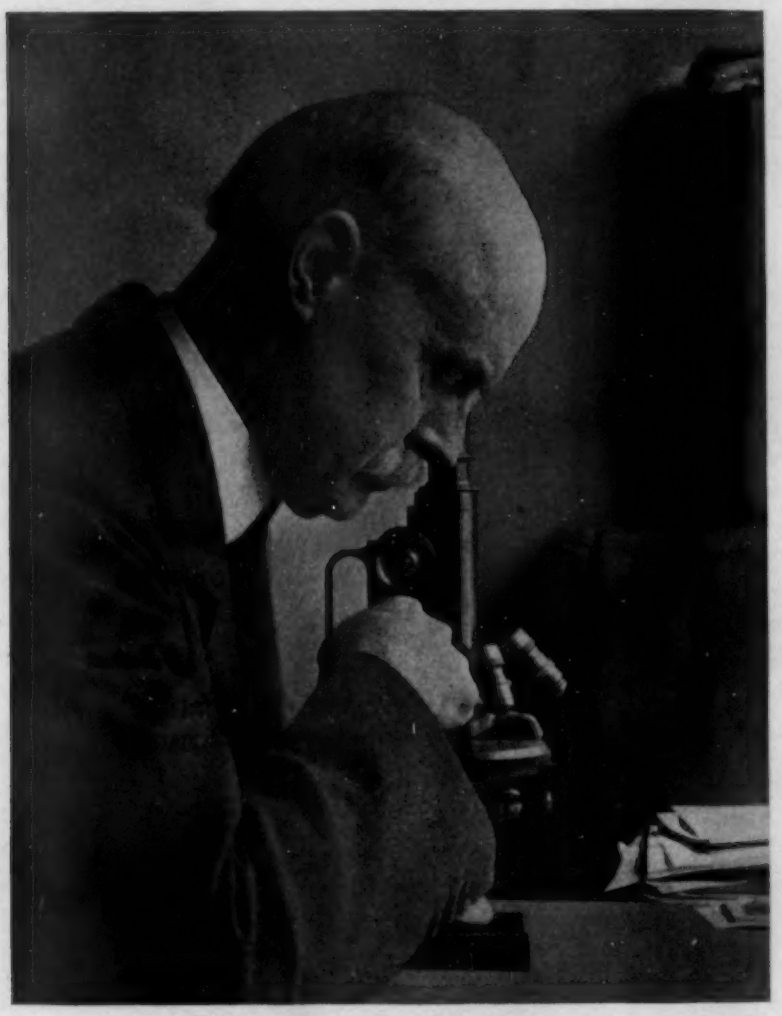
Frank Burr Mallory died on Sept. 27, 1941, at the age of 78, at his home in Brookline, Mass. He was born in Cleveland in 1862. He graduated from Harvard College in 1886 with the degree of Bachelor of Arts and from Harvard Medical School in 1890 with the degrees of Master of Arts and Doctor of Medicine. In the same year, he joined the teaching staff of his alma mater as assistant in histology, and became assistant in pathology the following year. He was made assistant professor of pathology in 1896, associate professor in 1901 and professor in 1928. In 1932 he retired from this position, becoming emeritus professor. In 1891 he joined the staff of the pathologic laboratory of the Boston City Hospital. In 1908 he was appointed pathologist to that institution. On reaching the age limit in 1932, he retired, receiving the title of consulting pathologist. Dr. Mallory spent the year from 1893 to 1894 with Chiari in Prague, Czechoslovakia, and Ziegler in Freiburg, Germany.

Dr. Mallory was treasurer of the American Association of Pathologists and Bacteriologists from 1911 to 1940. He also was a past president of this society. He served as editor in chief of the *Journal of Medical Research* from 1923 to 1925, and when in that year that journal became the *American Journal of Pathology* he continued as editor in chief until 1940. He was a member of numerous American scientific societies and, in addition, was a corresponding member of the Royal Medical Society of Budapest, Hungary, a member of the Deutsche Pathologische Gesellschaft and an honorary member of the Pathological Society of Great Britain and Ireland.

Dr. Mallory was one of the leading spirits in the formation of the American Association of Pathologists and Bacteriologists. It is interesting to recall that this project was opposed by practically all the older pathologists, who felt that the Association of American Physicians was "*the* pathological society" and that no other organization was needed. Dr. Mallory nevertheless persisted in his support of the formation of this new organization and carried with him the younger men in Boston. He, together with Gaylord, Weil and a few others, was responsible for the creation of the American Association for Cancer Research. Further-

more, the activities of this same group aided in the organization of the American Society for the Control of Cancer.

The American Association of Physicians awarded the Kober medal to Dr. Mallory in 1935 for outstanding service in pathology. In the



Frank B. Mallory

1862—1941

same year he was presented the gold-headed cane given to the American Association of Pathologists and Bacteriologists by Dr. Harold C. Ernst to be awarded for special merit. Tufts College bestowed the honorary

degree of Doctor of Science on him in 1928, and Boston University conferred a similar degree on him in 1932.

In 1897 Dr. Mallory with J. Homer Wright published "Pathological Technique," which has been a standard laboratory guide since its first appearance.[1] His "Principles of Pathologic Histology" appeared in 1914, a book characterized by the clarity of its text, its original ideas and the beauty of its illustrations.[2] In his later years, he was working on a revised and greatly expanded edition, but this work was interrupted by his illness.

Dr. Mallory was keenly interested in pathology, especially in its histologic aspects. While he respected the literature, he felt progress was to be made through direct personal observations. He stated this point of view in the introduction to his "Principles of Pathologic Histology" as follows:

> . . . In pathology the lesions themselves are the original sources of information. . . . The literature of a pathologic subject represents the history of the study, understanding and interpretation of the lesions. It is much less important than the study of the lesions themselves. Hence, not the literature of a pathologic subject, but perfect tissue, fixed and stained by the best methods, affords the greatest opportunities for advance.

He had a profound contempt for what he termed "armchair" pathologists, meaning those who wrote textbooks of pathology based not on what they themselves had observed but on what they had read in the literature.

Among subjects of pathology in which Dr. Mallory was especially interested and on which he contributed much to the literature may be mentioned the classification of tumors, technical methods, cirrhosis of the liver and infectious diseases. Early in his career he showed a keen interest in histopathologic technic, and he developed many new staining methods which are in wide use today. Furthermore, he always emphasized the importance of exactness and attention to detail in carrying out technical procedures and insisted on the maintenance of high standards in his own laboratory. As James Ewing so emphatically described this aspect in his presentation speech of the Kober medal:

> . . . A foremost factor in his training was his superb technique, which greatly enlarges the significance of the morphology of disease, and, indeed, opens up a new world, which is closed to the indifferent technician. The older pathologists had largely exhausted the possibilities of pathological anatomy and histology, but it remained for men like Mallory, Ramón y Cajal and del Río Hortega to carry histopathology to its highest development, and to make contributions beyond the reach of other methods.

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1. Mallory, F. B., and Wright, J. H.: Pathological Technic, Philadelphia, W. B. Saunders Company, 1897.

2. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914.

In addition to his scientific work, Dr. Mallory made an outstanding contribution to medicine in the training of young men. The number of graduates of the laboratory from 1895 to 1932 numbered approximately 125. Many of these men have been outstanding in the clinical branches of medicine as well as in pathology.

Dr. Mallory always took a great interest in the members of his staff and their contact with him was close. He was genuinely fond of many of them, and this feeling was warmly reciprocated. He was interested not only in their scientific training and advancement but also in their personal lives. He did not hesitate, on occasions, to administer reproof and advice with parental force and Mallory thoroughness. Those who received such attention from Dr. Mallory now, with affectionate amusement and gratitude, recall him in stern or even irate mood, surrounded by jars and fumes of formaldehyde in the storage room, which was also dedicated to departmental *mores*. An invitation to Sunday dinner and a two hour walk in the suburbs of Boston usually followed such disciplinary attention. He was always pleased to have former members of his staff return to visit him, and no matter how busy he might be, he willingly dropped his work in order to see them. His influence on his assistants both during their term of service and later was great, and through them, was felt throughout the country.

Dr. Mallory was endowed with boundless energy and enthusiasm for his life work. He was truly devoted to pathology in all its aspects, and neither increasing age nor infirmity decreased his interest in any way. After retiring in 1932, he continued to come to the laboratory as regularly as he always had and to work as industriously. When he was compelled by ill health to leave the laboratory last February, he was actively engaged in experimental work in connection with cirrhosis of the liver. Such enthusiasm and interest as was his had a profound and inspiring influence on his staff.

The present pathologic laboratory of the Boston City Hospital was named the Mallory Institute of Pathology by the trustees of the hospital as an expression of their appreciation of the many years he had so faithfully served the hospital.

Dr. Mallory is survived by a sister, Miss M. Eleanor Mallory, and by two sons, Dr. Tracy B. Mallory and Dr. G. Kenneth Mallory.

The death of Dr. Mallory has removed from the world of science an outstanding figure. To his friends and former associates, it has meant an irreplaceable loss.

FREDERIC PARKER JR.

Book Reviews

Immunity Against Animal Parasites. James T. Culbertson, assistant professor of bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 274, with 4 figures. Price $3.50. New York: Columbia University Press, 1941.

The present volume is particularly significant because it is the first comprehensive treatment of the field since the publication of Taliaferro's "The Immunology of the Parasitic Infections" in 1929. The author takes the latter monograph as his point of departure and except for a few earlier references limits his account to a review of the significant studies since 1929. He assumes that the reader is well prepared in both parasitology and immunology and hence makes no pretense of presenting the life cycles of the parasites or the general principles of immunology.

After an introduction which consists mainly of a brief historical outline, the book is divided into three sections. The first section on natural resistance and acquired immunity, composed of eight chapters, gives the experimental basis and a theoretic discussion of natural resistance, age resistance and specifically acquired immunity and describes the requisites for the immune response, the parasites which elicit immunity, the mechanisms of specific immunity and the methods of demonstrating immunity. The second section, comprising nine chapters, gives a discussion of immunity in the specific diseases and infections produced by the animal parasites, including the arthropods. The third section, entitled "Aplied Immunology," consisting of three chapters, is a consideration of classification of parasites, vaccination against parasites and diagnosis of parasitic infections. The author has succeeded admirably in his avowed purpose of writing for such a diversified group as beginning students, trained investigators and practicing physicians and veterinarians.

At times the reader may feel that the deliberate attempt of the author to reduce to a minimum personal concepts, both his own and others, has resulted in too little criticism of the conclusions of others and in too little of the author's own theoretic concepts, both of which might have been of considerable help in correlating some of the experimental findings. Such a criticism is minor and does not lessen the indebtedness of workers in this field to the author for his collection of the extensive literature and for his thorough and excellent review of a rapidly advancing subject.

Surgery of the Heart. E. S. J. King, M.D., M.S., D.Sc. (Melbourne), F.R.C.S. (England), F.R.A.C.S., Major A.A.M.C., honorary surgeon to outpatients, Royal Melbourne Hospital; Jacksonian prizeman, Royal College of Surgeons; sometime Stewart and senior lecturer in pathology and Stewart scholar in surgery, University of Melbourne. Pp. 728, with 268 figures. Price $13.50. Baltimore: Williams & Wilkins Company, 1941.

This book received the Jacksonian prize of the Royal College of Surgeons in 1938. It is based on the author's clinical, pathologic and experimental work coupled with a thorough study of the literature on cardiac surgery. The first section, 185 pages, reviews the development, anatomy, physiology and pathology of the heart, with consideration of radiology and electrocardiography. The second section, which covers more than 500 pages, deals with "the methods of surgical approach to the heart and various operative procedures, including the anatomical structures and physiological principles on which they are based. The extensive experimental work is then reviewed, and finally the diseases of the heart are described and their suitability or otherwise for surgical treatment discussed." The succinct summaries here and there of the historical developments in the surgical

treatment of the pericardium, heart and great vessels are instructive and notably accurate. The diseases of the myocardium, the coronary vessels, the endocardium, the pericardium, the pulmonary vessels, the aorta and the venae cavae are considered in more or less detail. The operative and experimental procedures are clearly described. Numerous photographs, drawings and tracings illustrate the presentation. There are good illustrations in color of the cardiac vessels and their anastomoses, the cardiac innervation from the cervical nerves, and embolism of the pulmonary artery. There are lists of select references at the end of each subsection of the text. The bibliography of the surgical approach to heart disease fills 9 pages, that of injuries to the heart 22 and that of coronary occlusion 8. The American literature has been searched thoroughly. King's book will be a landmark in the literature on the surgery of the heart. It summarizes well the remarkable developments in that field and points the way to further advances.

Diseases of the Blood and Atlas of Hematology, with Clinical and Hematologic Descriptions of the Blood Diseases Including a Section on Technic and Terminology. Roy R. Kracke, M.D., professor of bacteriology, pathology and laboratory diagnosis, Emory University School of Medicine; pathologist to the Emory University Hospital; consultant in hematology to the Grady Hospital and Eggleston Hospital for Children, Atlanta, Ga.; formerly, director of the Hematological Registry, American Society of Clinical Pathologists. Second edition, thoroughly revised, reset and enlarged. Pp. 692, with 54 color plates and 46 other illustrations. Price $15. Philadelphia, London, Montreal: J. B. Lippincott Company, 1941.

The first edition was published in 1937 and was favorably received (see a review in the ARCHIVES OF PATHOLOGY [**25**:442, 1938]). The call for a second edition indicates that the book has fulfilled a need in the field described by its title. The new edition has been carefully revised and brought up to date. It is larger than the first edition by 160 pages. Certain omissions in the first issue have been remedied, new chapters have been added on hemolytic anemia, hemoglobinuria, vitamin K and the treatment of leukemia. In this last chapter, which is written by Lloyd Carver, the recent developments in the treatment of leukemia by radiation and by radioactive isotopes are described. The chapter on blood transfusion (Francis P. Parker) covers well all details of that procedure as practiced at this time. Ten new colored drawings have been added, and also 29 other new illustrations. The colored drawings are uniformly excellent. The 54 plates make up a good atlas of the morphology of the blood. The chapter on the marrow (R. P. Custer) is well illustrated. Probably fetal erythroblastosis deserves more attention than it receives. The difference between fetal and postfetal hemoglobin and its possible significance are not discussed. Experimenters using laboratory animals will find the chapter on the blood of such animals, illustrated by plate 53, helpful